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(54) **BAROREFLEX THERAPY FOR DISORDERED BREATHING**

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(21) Appl. No.: **10/864,070**

(22) Filed: **Jun. 8, 2004**

Related U.S. Application Data

(62) Division of application No. 10/746,844, filed on Dec. 24, 2003.

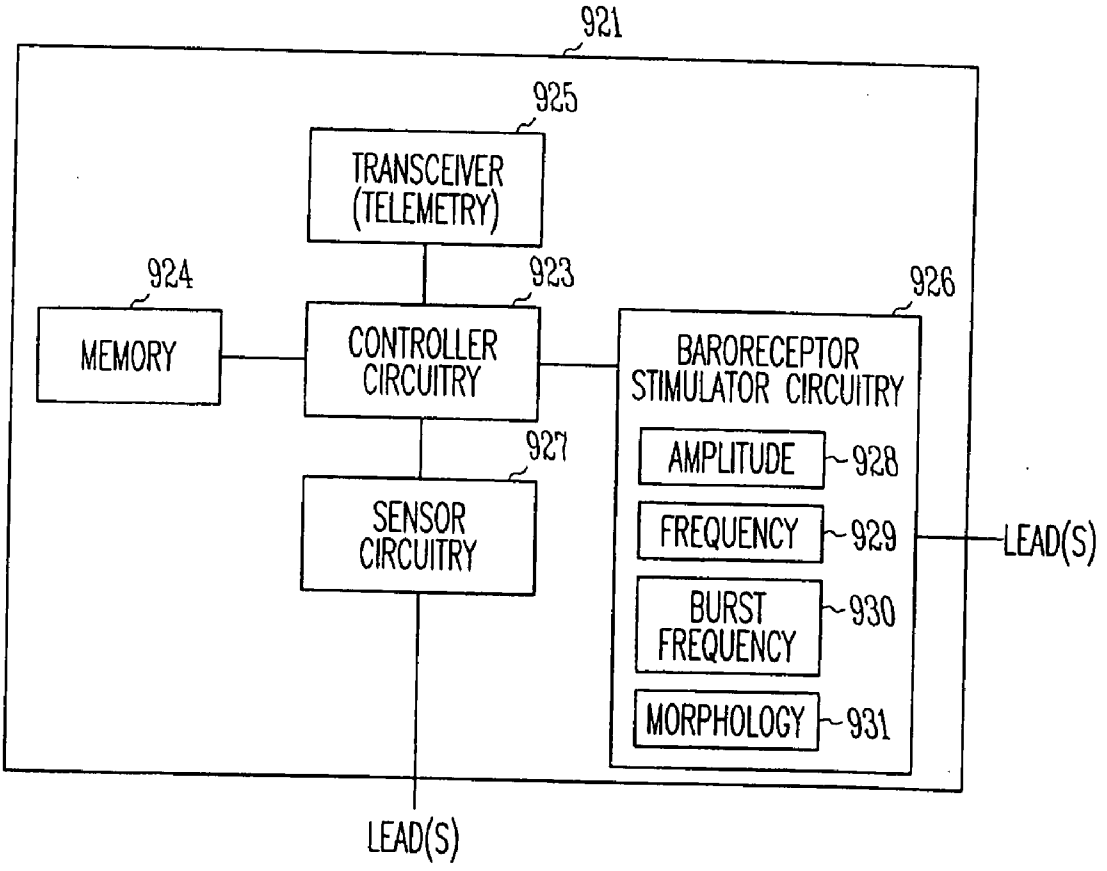
Publication Classification

(51) **Int. Cl.**[7] **A61N 1/18**

(52) **U.S. Cl.** **607/42**

(57) **ABSTRACT**

An aspect of the present subject matter relates to a baroreflex stimulator. An embodiment of the stimulator comprises a pulse generator to provide a baroreflex stimulation signal through an electrode, and a modulator to modulate the baroreflex stimulation signal based on a circadian rhythm template. Other aspects are provided herein.



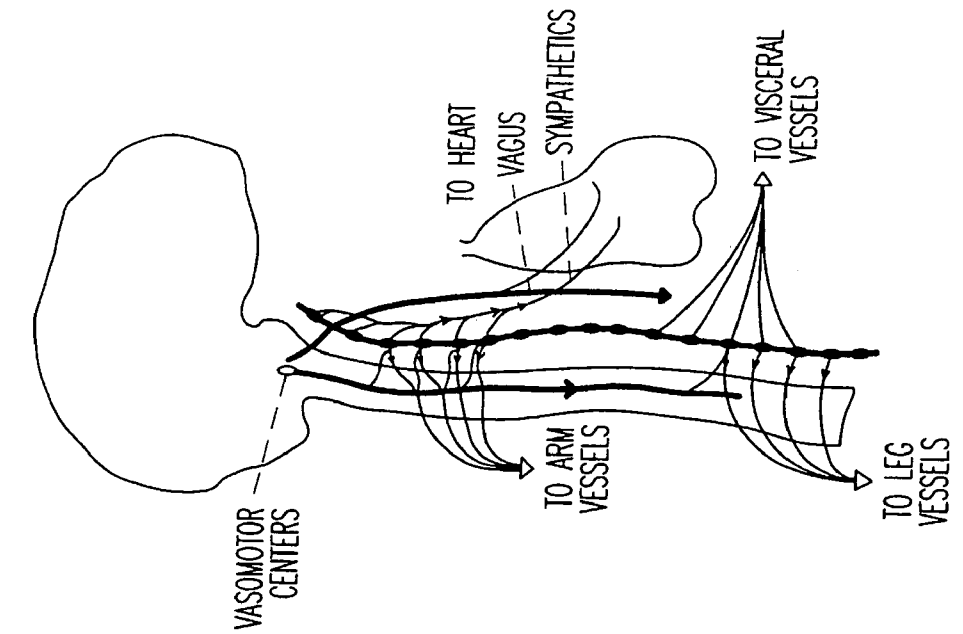

VASOMOTOR CENTERS
TO HEART
VAGUS
SYMPATHETICS
TO ARM VESSELS
TO VISCERAL VESSELS
TO LEG VESSELS

Fig. 1B

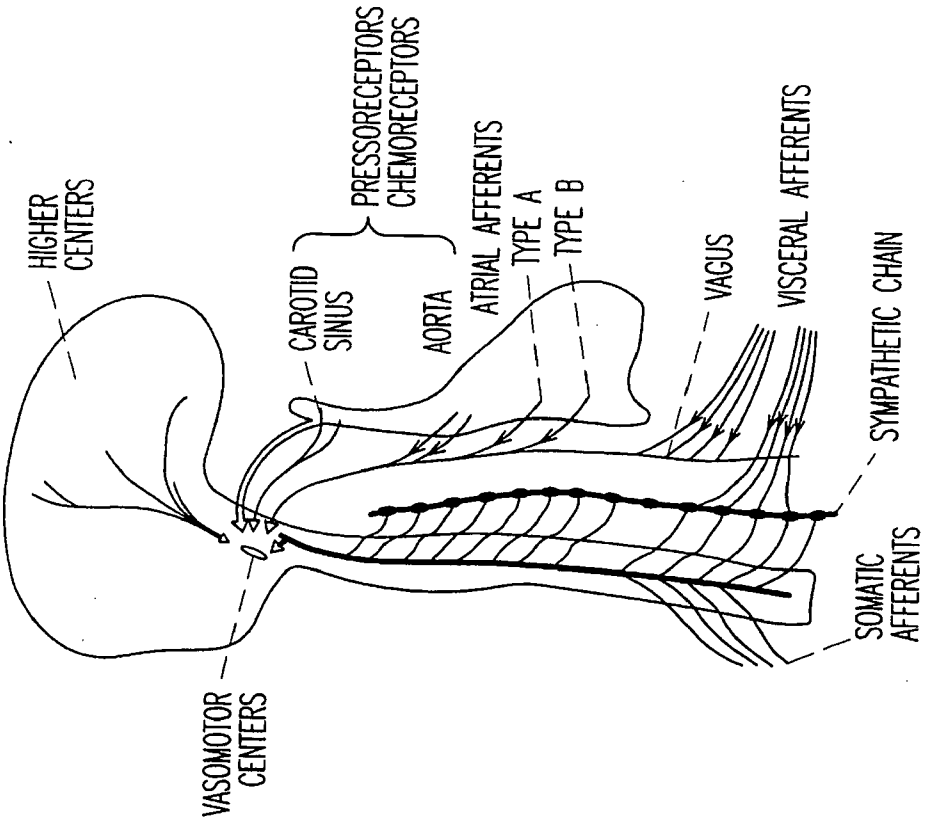

HIGHER CENTERS
CAROTID SINUS
AORTA
PRESSORECEPTORS
CHEMORECEPTORS
ATRIAL AFFERENTS
TYPE A
TYPE B
VAGUS
VISCERAL AFFERENTS
SYMPATHETIC CHAIN
SOMATIC AFFERENTS
VASOMOTOR CENTERS

Fig. 1A

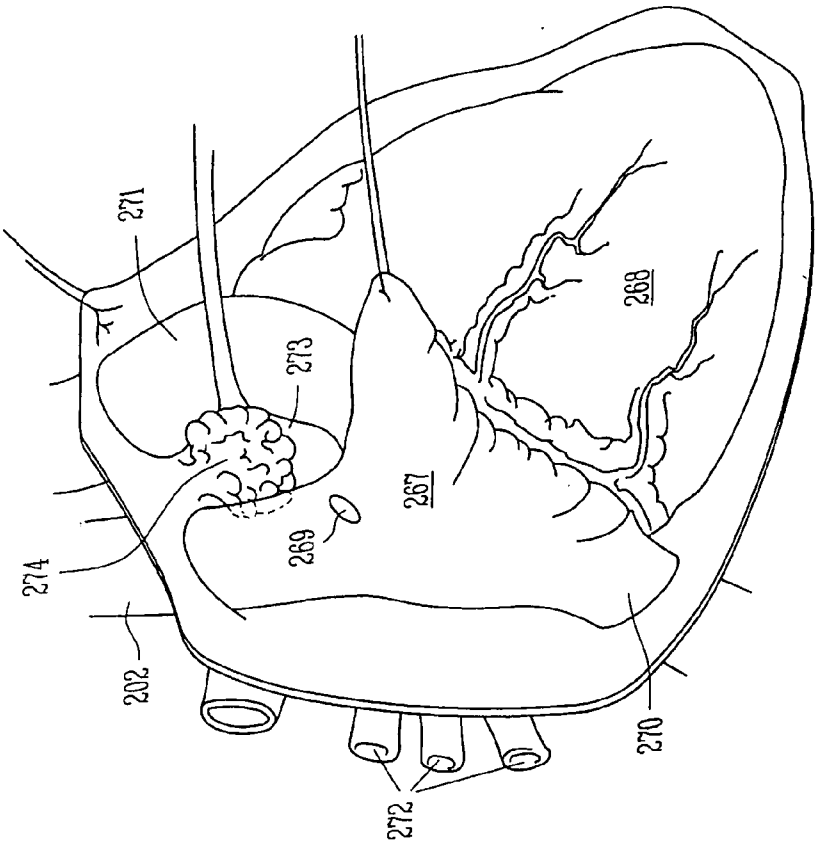


Fig. 2B

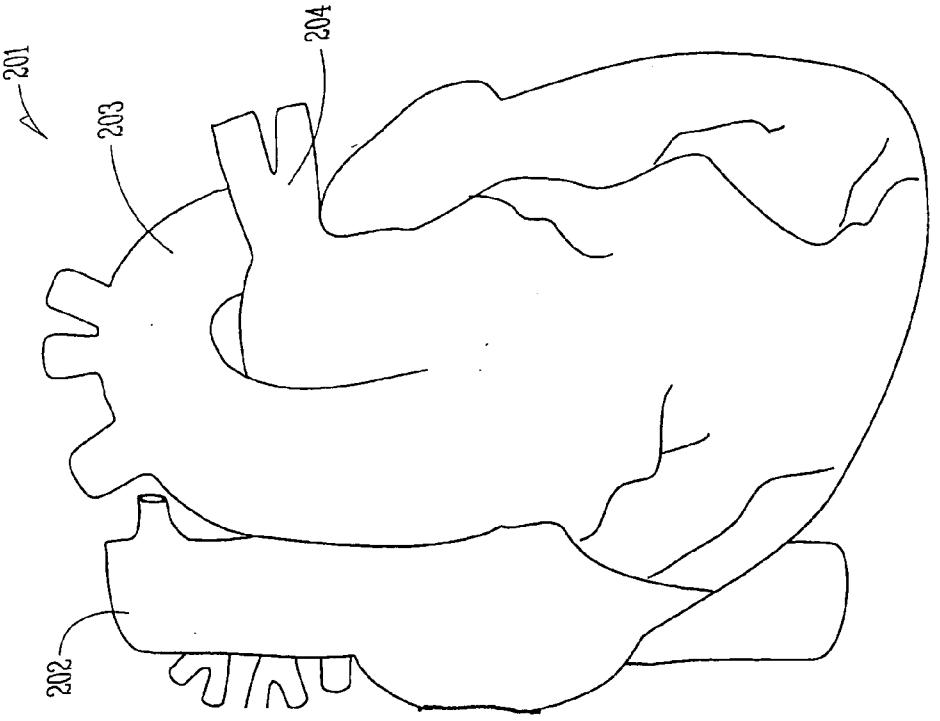


Fig. 2A

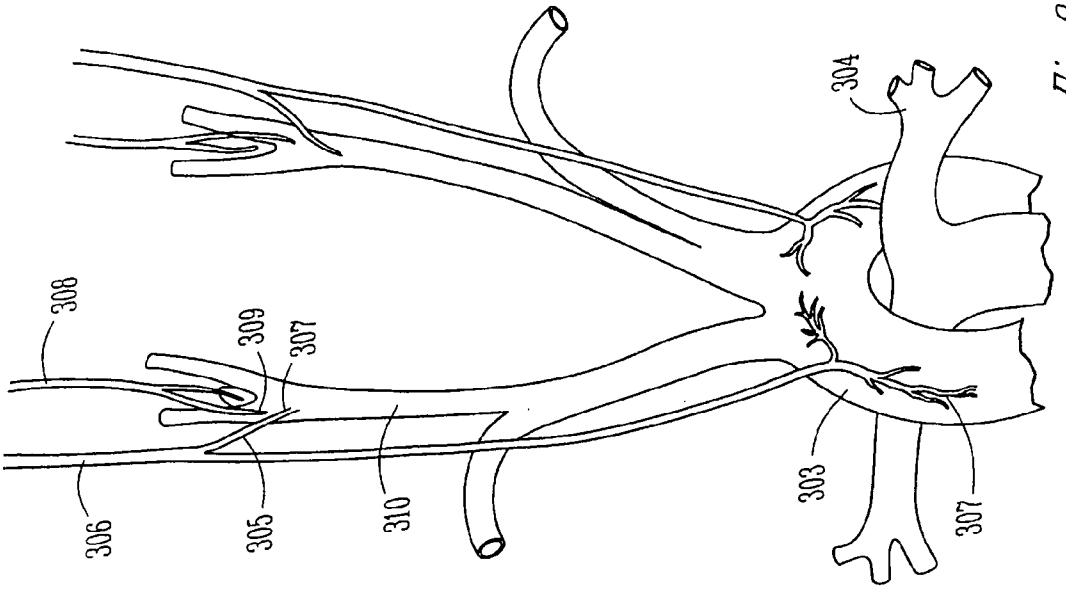

304
308
309
307
306
305
310
303
307

Fig. 3

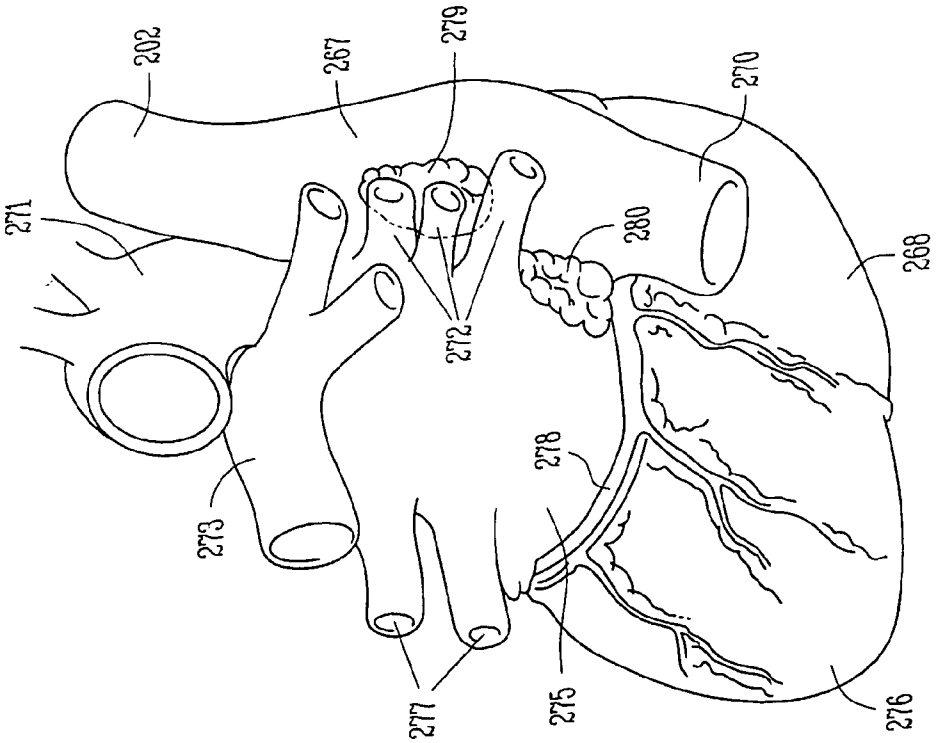

202
267
279
270
271
280
268
272
278
273
277
275
276

Fig. 2C

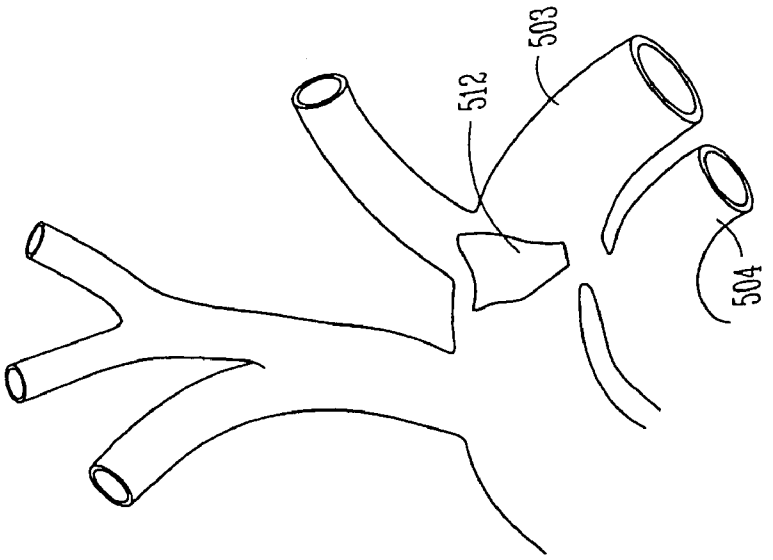


Fig. 5

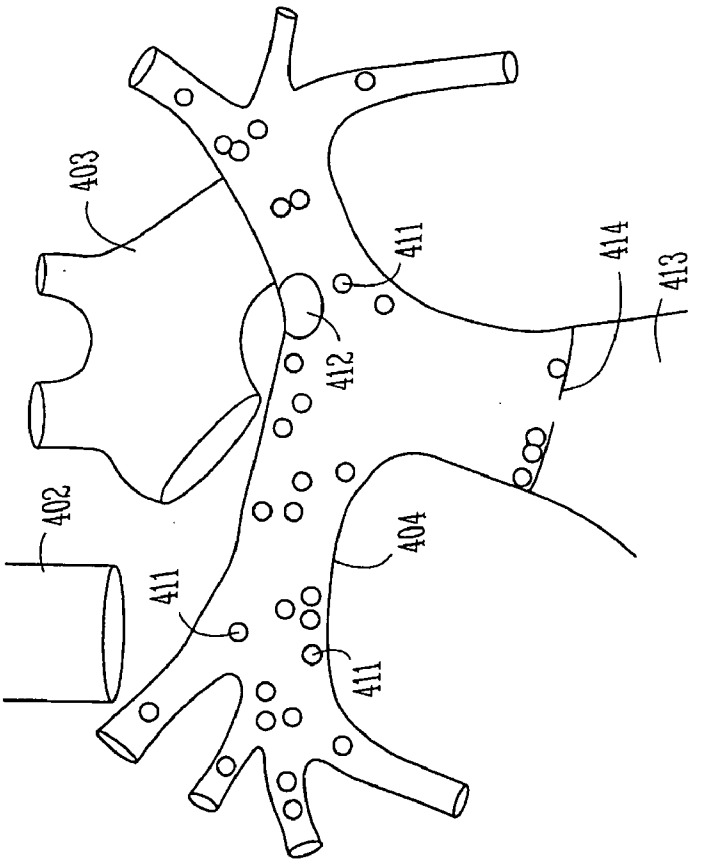


Fig. 4

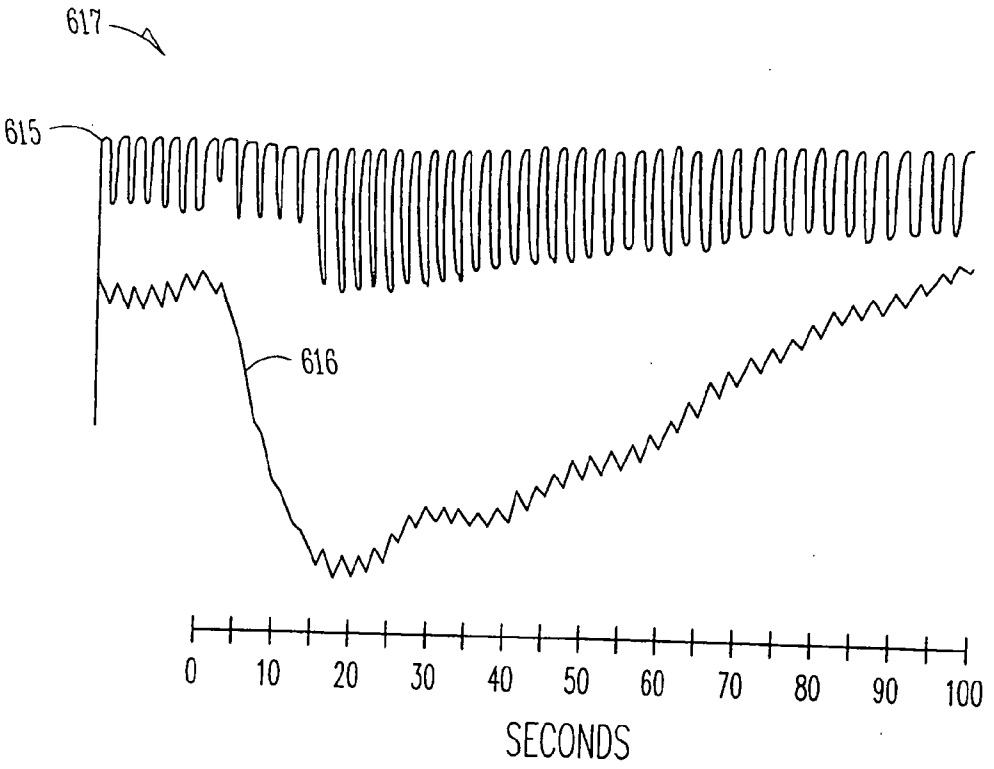

617
615
616
0
10
20
30
40
50
60
70
80
90
100
SECONDS

Fig. 6

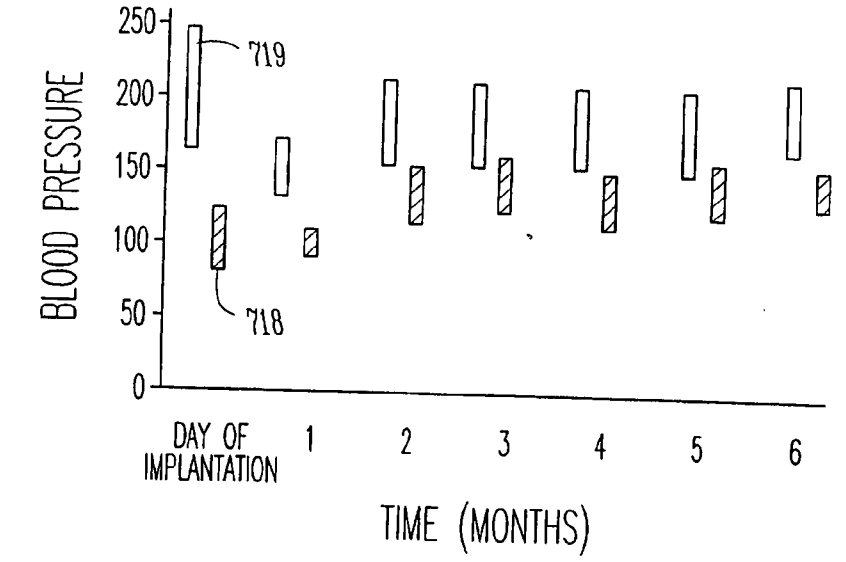

250
200
150
100
50
0
BLOOD PRESSURE
719
718
DAY OF IMPLANTATION
1
2
3
4
5
6
TIME (MONTHS)
CONTROL
STIMULATION

Fig. 7

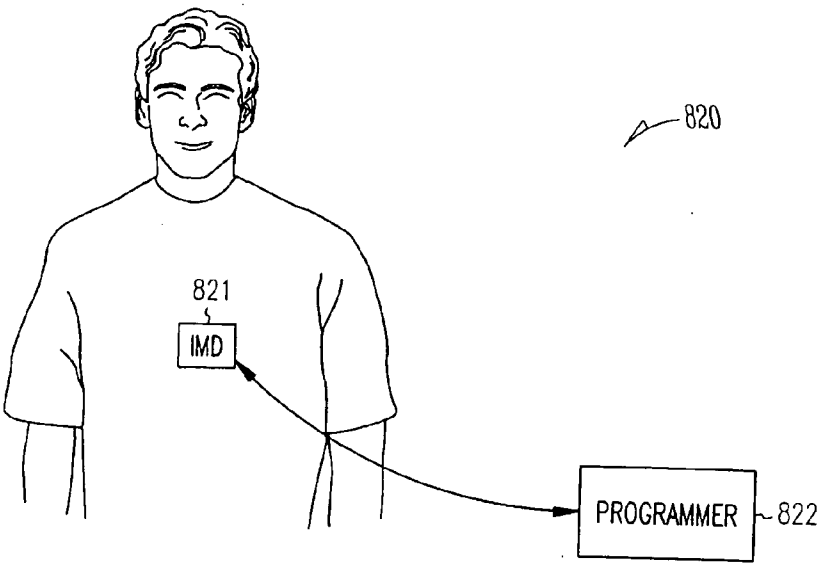

820
821
IMD
PROGRAMMER
822

Fig. 8

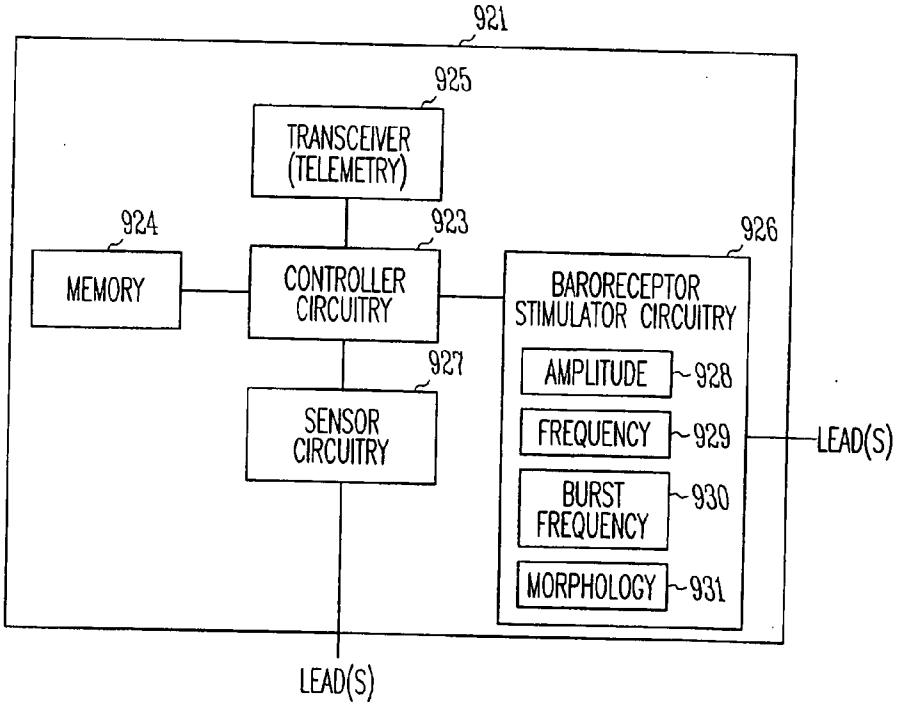

921
925
TRANSCEIVER (TELEMETRY)
924
MEMORY
923
CONTROLLER CIRCUITRY
926
BARORECEPTOR STIMULATOR CIRCUITRY
AMPLITUDE
928
FREQUENCY
929
BURST FREQUENCY
930
MORPHOLOGY
931
927
SENSOR CIRCUITRY
LEAD(S)
LEAD(S)

Fig. 9

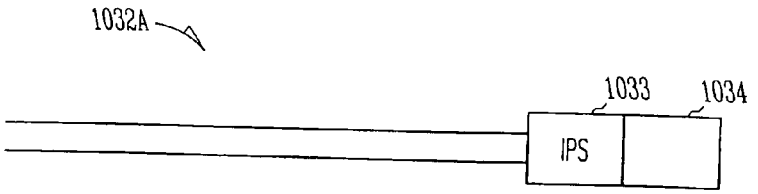


Fig. 10A

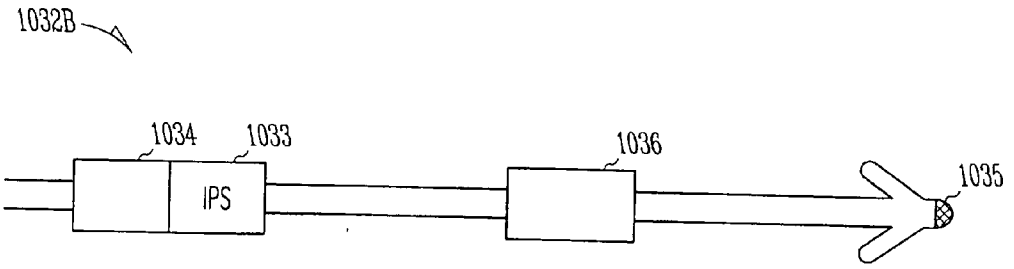


Fig. 10B

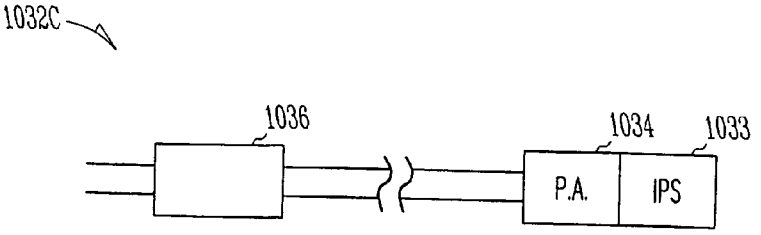


Fig. 10C

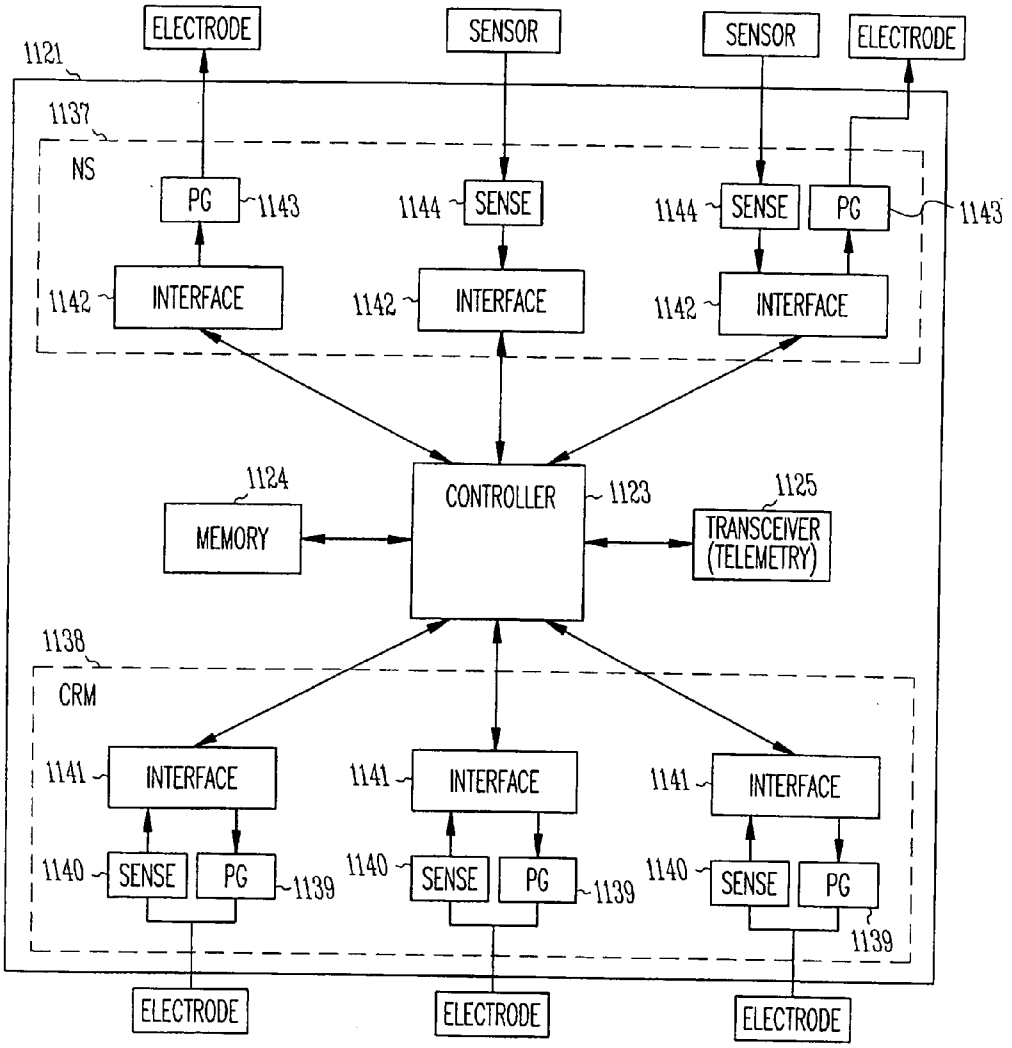

ELECTRODE
SENSOR
SENSOR
ELECTRODE
1121
1137
NS
PG
1143
1144
SENSE
1144
SENSE
PG
1143
1142
INTERFACE
1142
INTERFACE
1142
INTERFACE
1124
MEMORY
CONTROLLER
1123
1125
TRANSCEIVER (TELEMETRY)
1138
CRM
1141
INTERFACE
1141
INTERFACE
1141
INTERFACE
1140
SENSE
PG
1139
1140
SENSE
PG
1139
1140
SENSE
PG
1139
ELECTRODE
ELECTRODE
ELECTRODE

Fig. 11

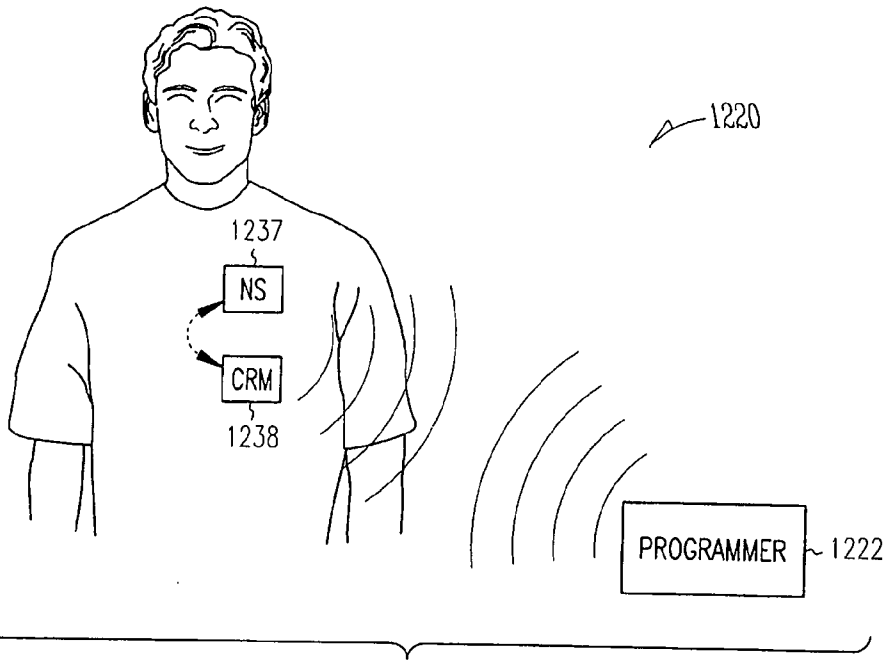

1220
1237
NS
CRM
1238
PROGRAMMER
1222

Fig. 12

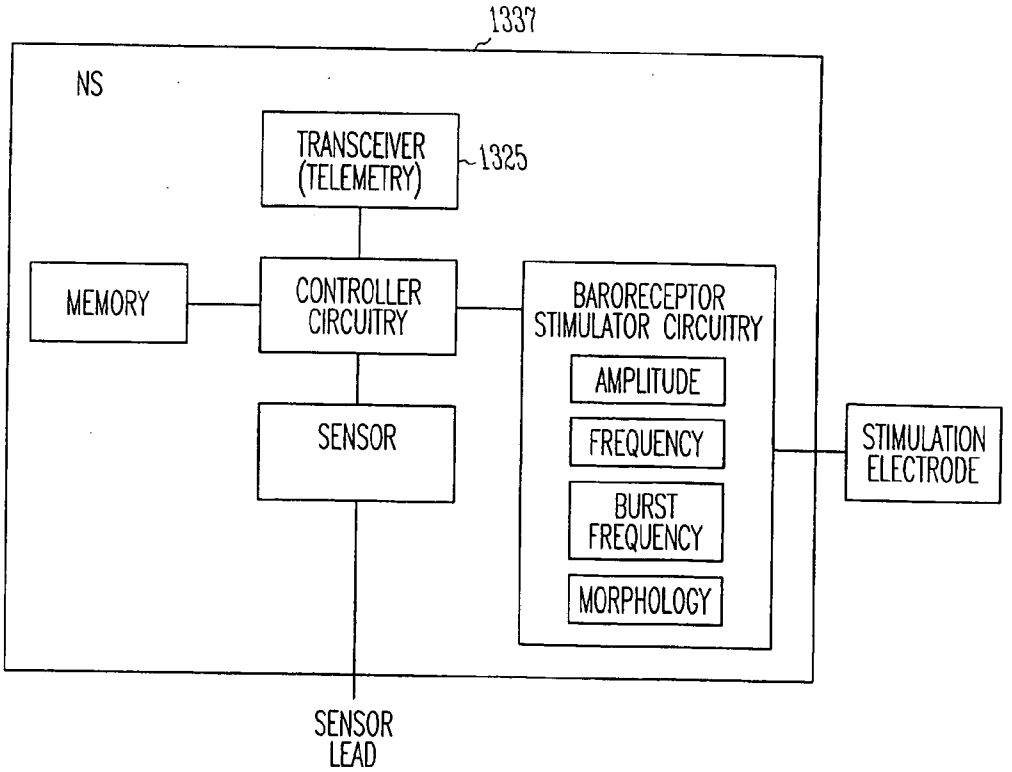

1337
NS
TRANSCEIVER (TELEMETRY)
1325
MEMORY
CONTROLLER CIRCUITRY
BARORECEPTOR STIMULATOR CIRCUITRY
AMPLITUDE
FREQUENCY
BURST FREQUENCY
MORPHOLOGY
SENSOR
STIMULATION ELECTRODE
SENSOR LEAD

Fig. 13

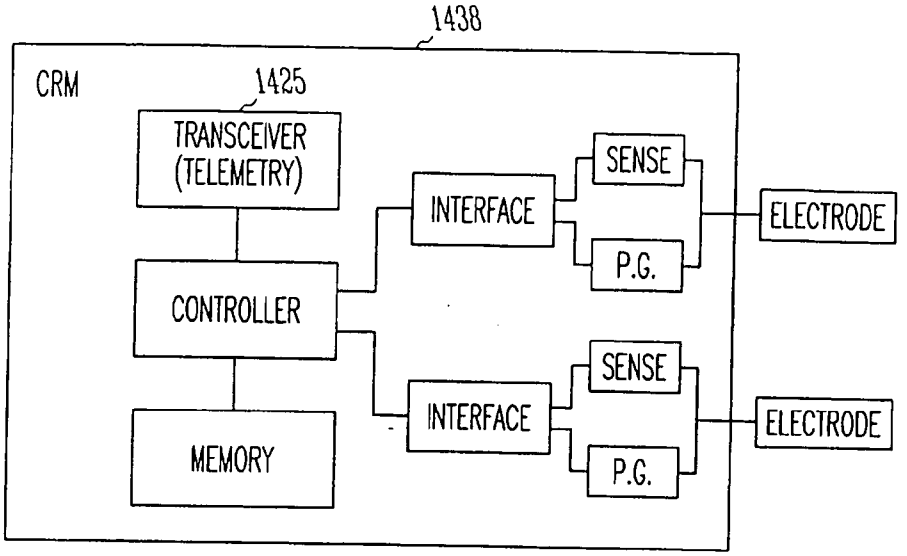

1438
CRM
1425
TRANSCEIVER (TELEMETRY)
CONTROLLER
MEMORY
INTERFACE
INTERFACE
SENSE
P.G.
SENSE
P.G.
ELECTRODE
ELECTRODE

Fig. 14

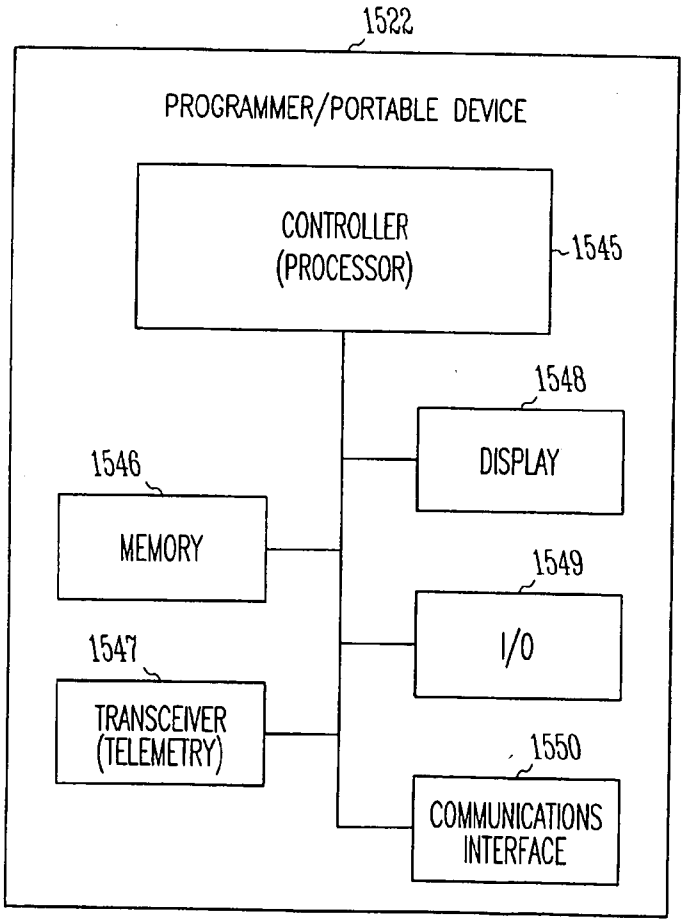

1522
PROGRAMMER/PORTABLE DEVICE
CONTROLLER (PROCESSOR)
1545
1548
DISPLAY
1546
MEMORY
1549
I/O
1547
TRANSCEIVER (TELEMETRY)
1550
COMMUNICATIONS INTERFACE

Fig. 15

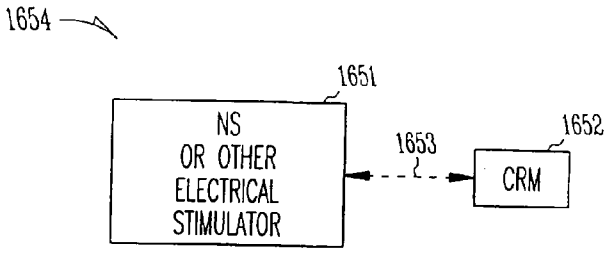


Fig. 16A

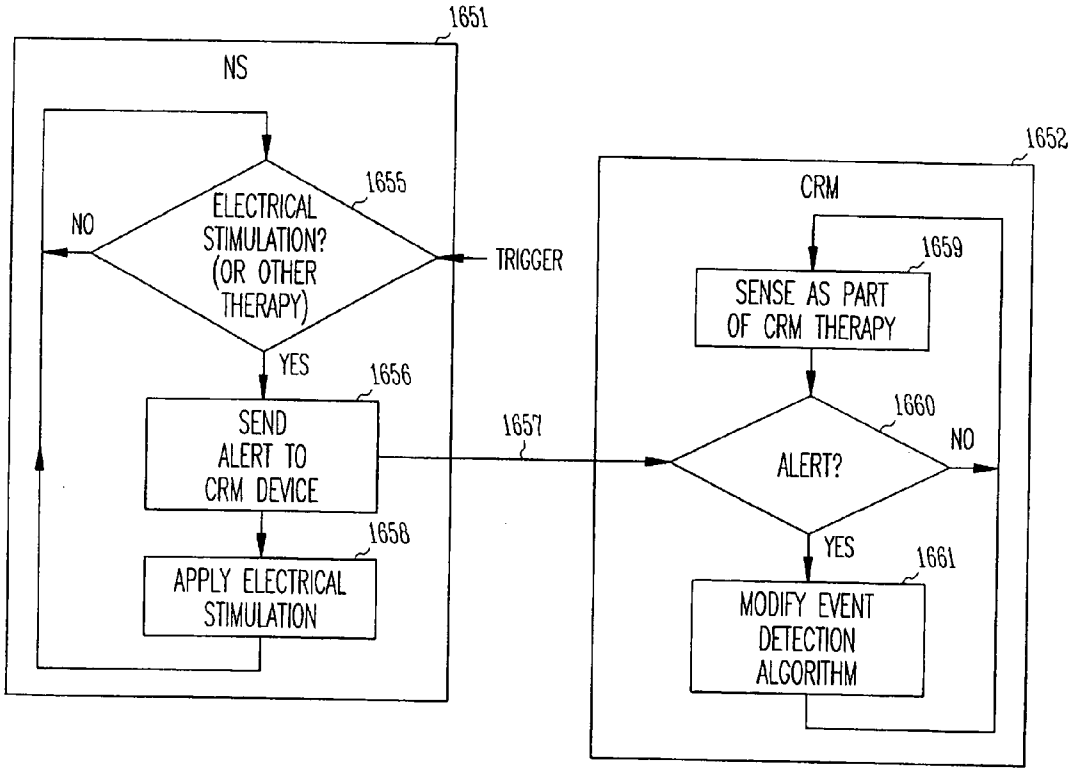


Fig. 16B

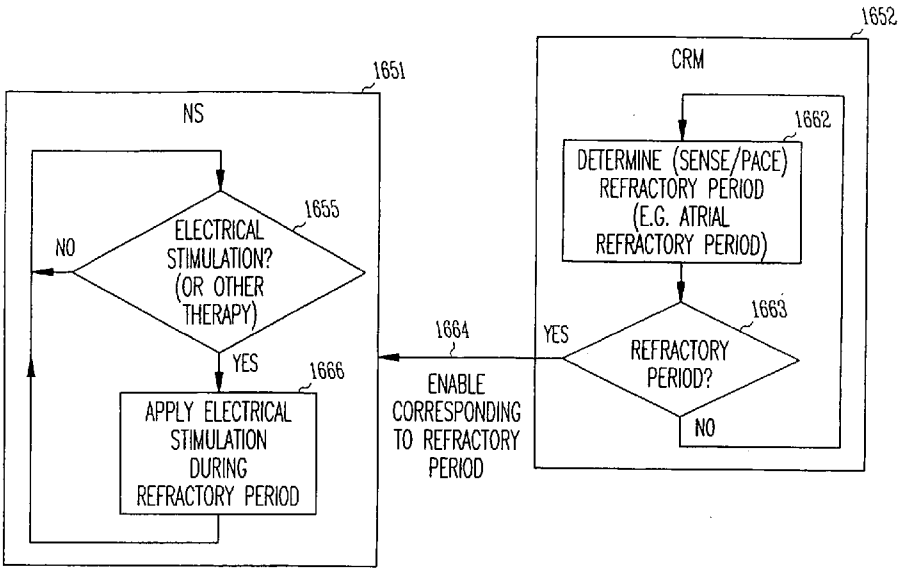


Fig. 16C

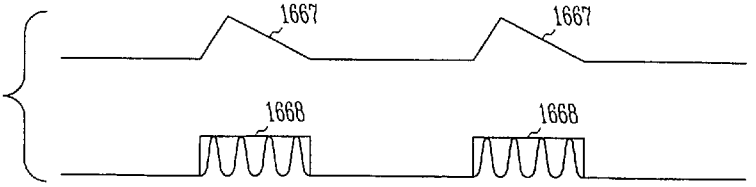


Fig. 16D

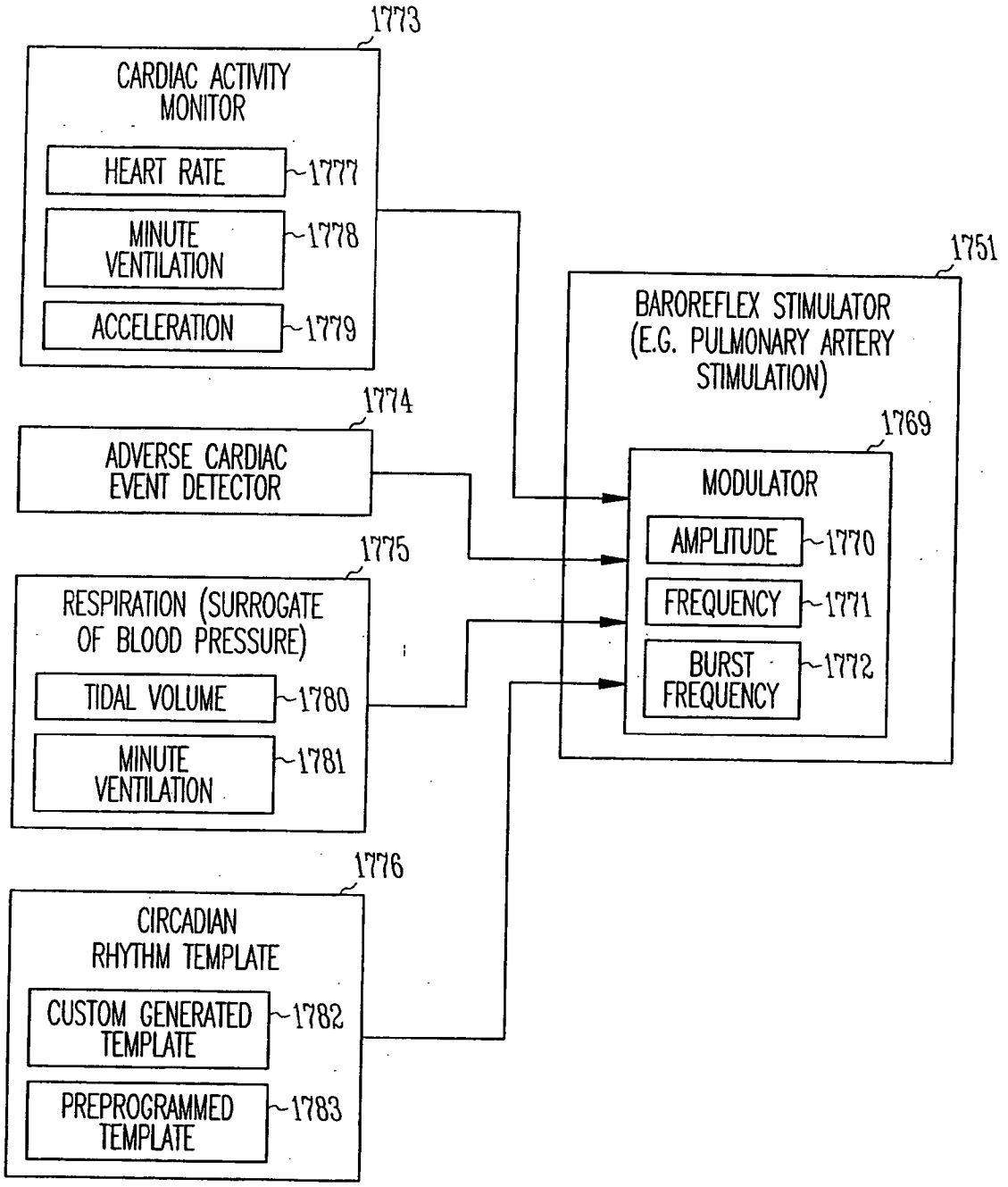

1773
CARDIAC ACTIVITY MONITOR
HEART RATE
1777
MINUTE VENTILATION
1778
ACCELERATION
1779
1751
BAROREFLEX STIMULATOR (E.G. PULMONARY ARTERY STIMULATION)
1769
MODULATOR
AMPLITUDE
1770
FREQUENCY
1771
BURST FREQUENCY
1772
1774
ADVERSE CARDIAC EVENT DETECTOR
1775
RESPIRATION (SURROGATE OF BLOOD PRESSURE)
TIDAL VOLUME
1780
MINUTE VENTILATION
1781
1776
CIRCADIAN RHYTHM TEMPLATE
CUSTOM GENERATED TEMPLATE
1782
PREPROGRAMMED TEMPLATE
1783

Fig. 17

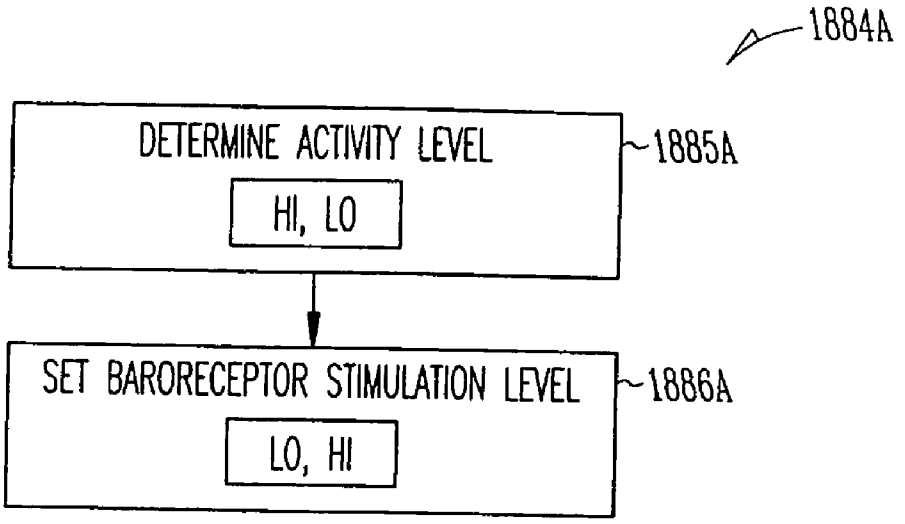


Fig. 18A

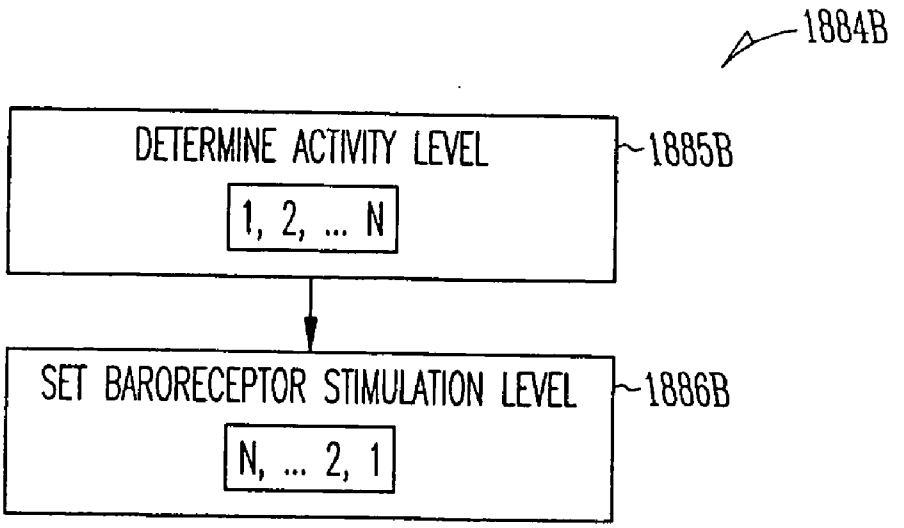


Fig. 18B

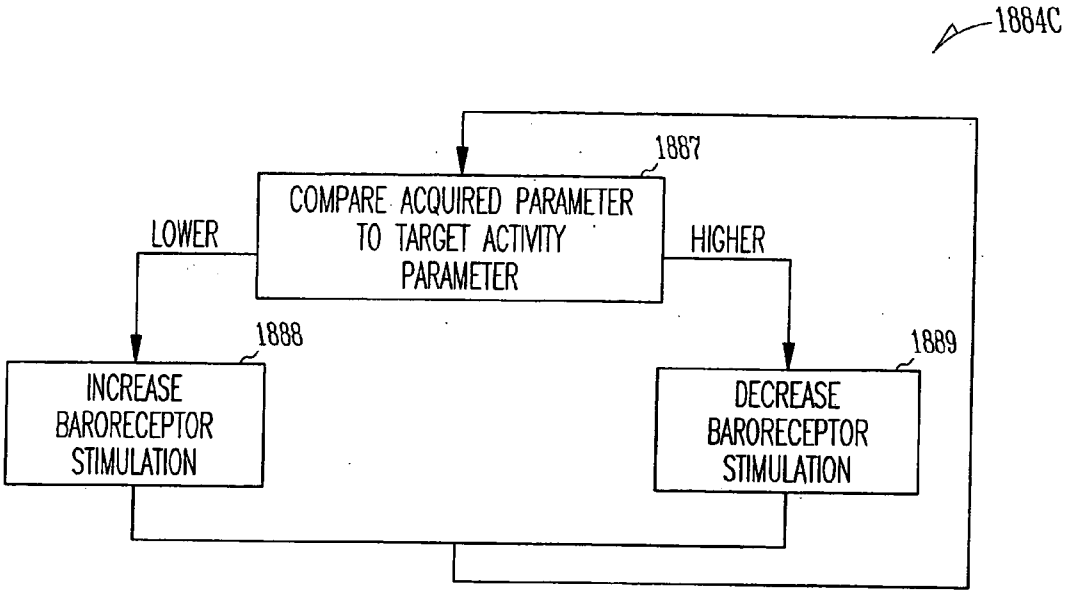


Fig. 18C

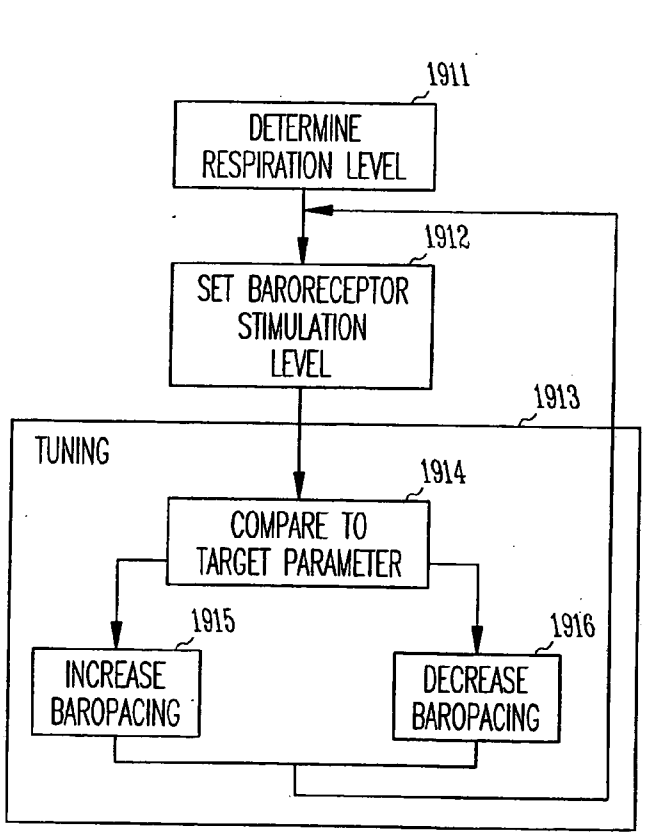


Fig. 19A

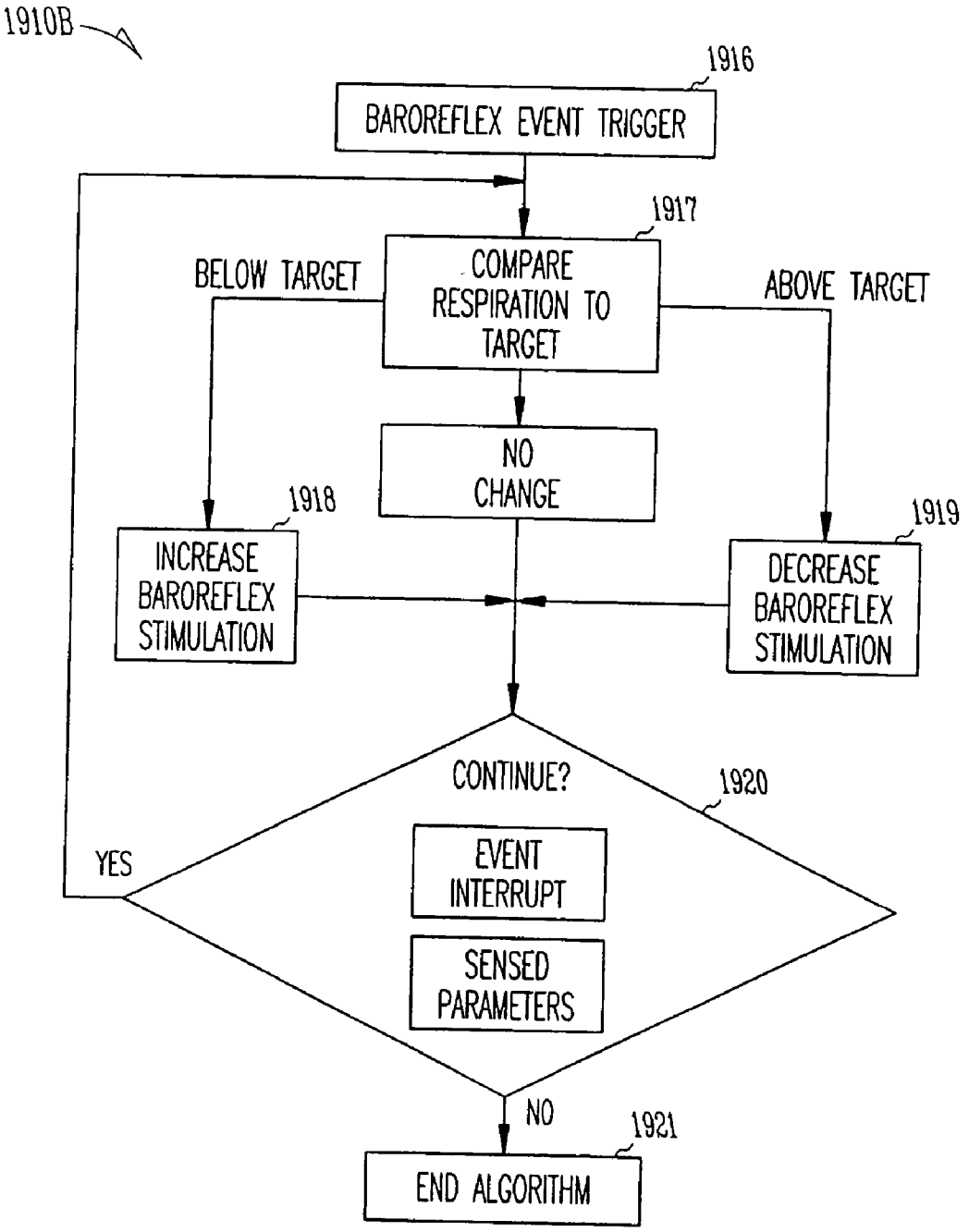

1910B
1916
BAROREFLEX EVENT TRIGGER
1917
COMPARE RESPIRATION TO TARGET
BELOW TARGET
ABOVE TARGET
NO CHANGE
1918
INCREASE BAROREFLEX STIMULATION
1919
DECREASE BAROREFLEX STIMULATION
CONTINUE?
1920
YES
EVENT INTERRUPT
SENSED PARAMETERS
NO
1921
END ALGORITHM

Fig. 19B

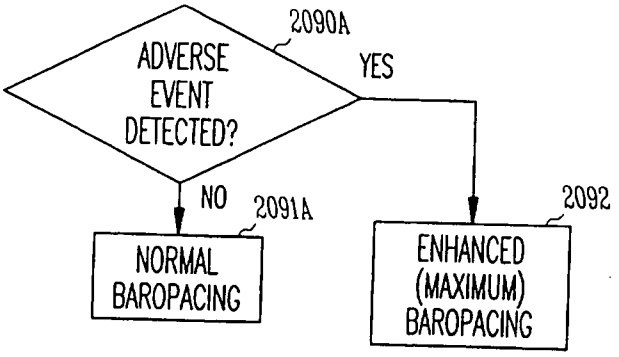


Fig. 20A

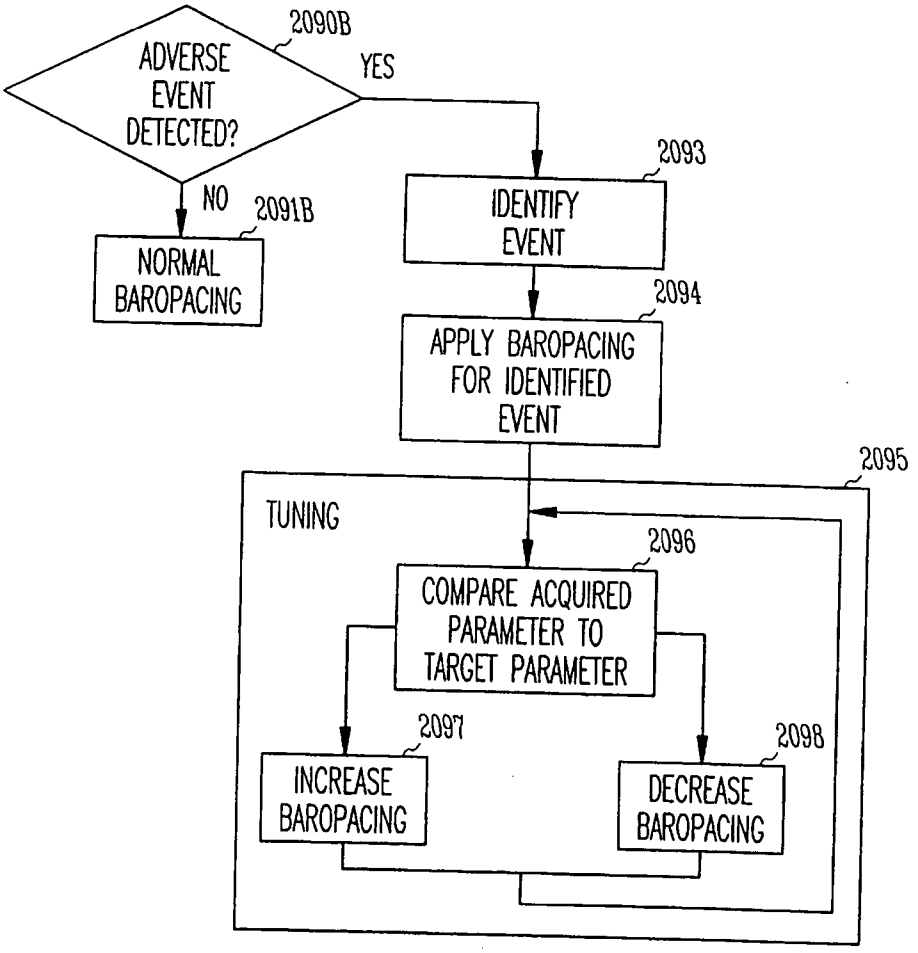


Fig. 20B

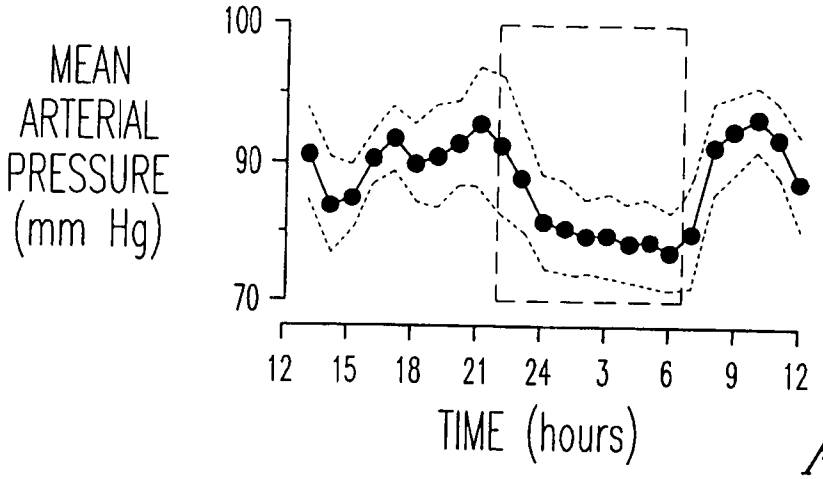


Fig.21A

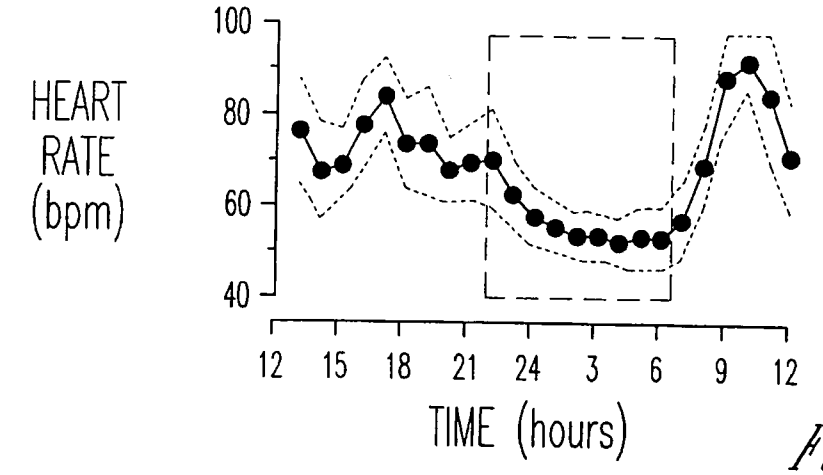


Fig.21B

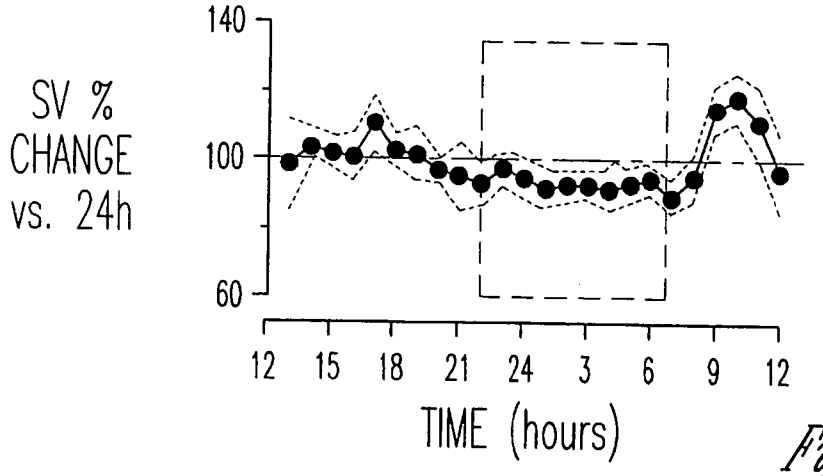


Fig.21C

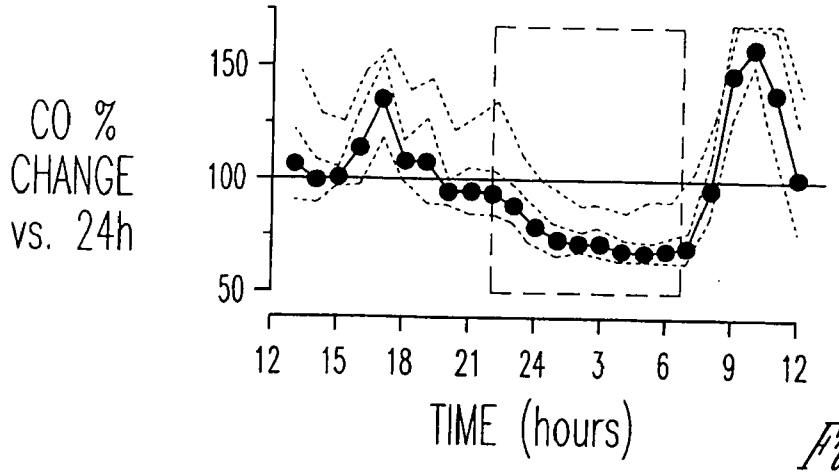


Fig.21D

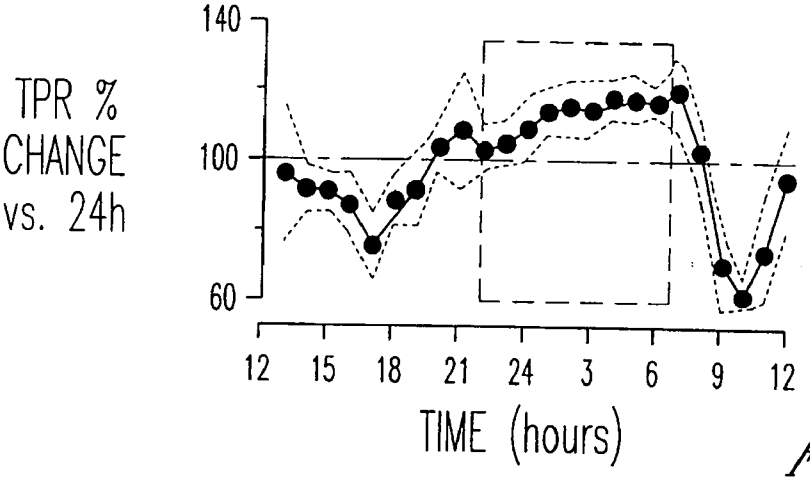


Fig.21E

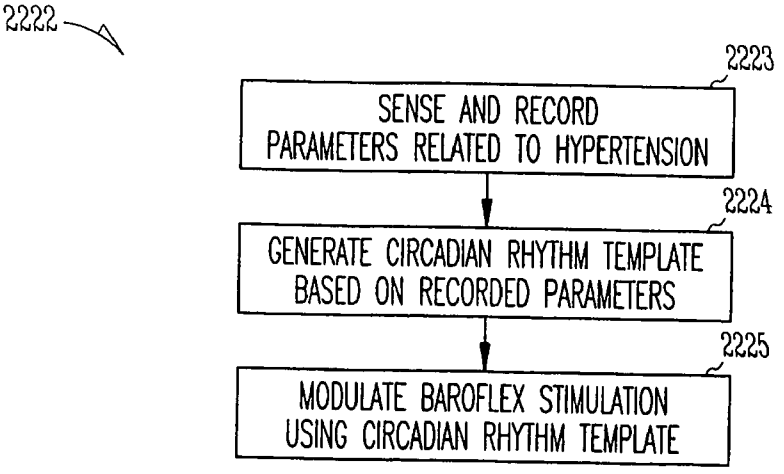


Fig.22

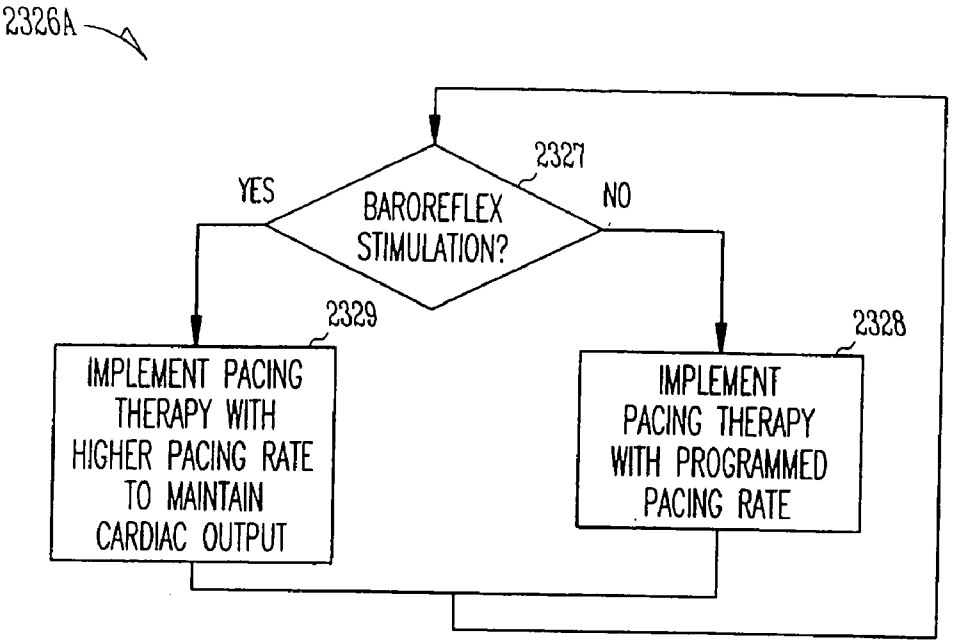


Fig. 23A

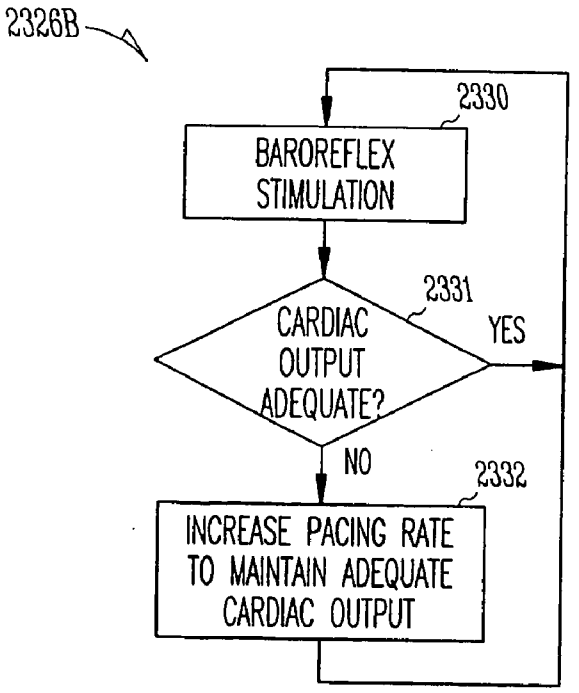


Fig. 23B

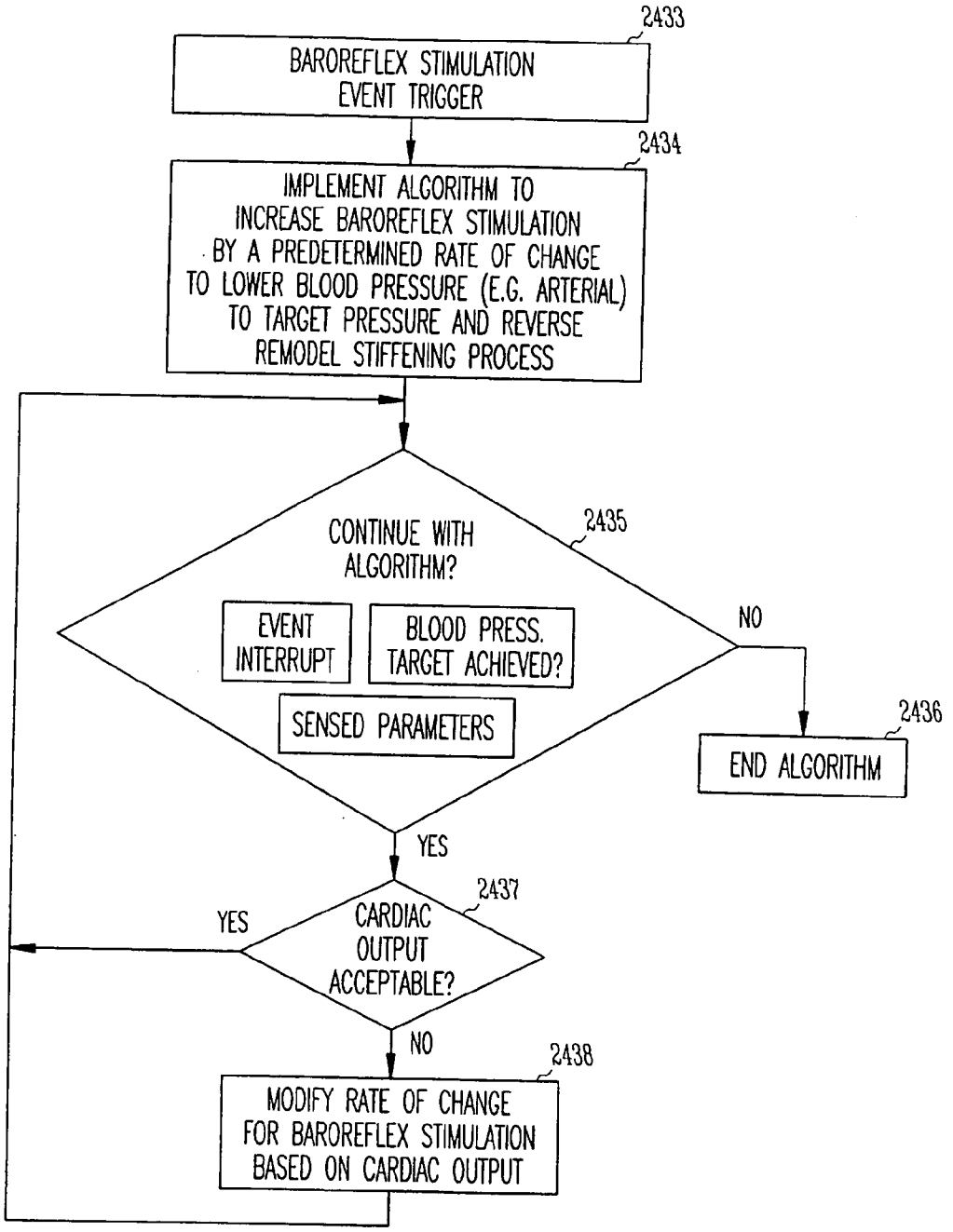

2433
BAROREFLEX STIMULATION EVENT TRIGGER
2434
IMPLEMENT ALGORITHM TO INCREASE BAROREFLEX STIMULATION BY A PREDETERMINED RATE OF CHANGE TO LOWER BLOOD PRESSURE (E.G. ARTERIAL) TO TARGET PRESSURE AND REVERSE REMODEL STIFFENING PROCESS
2435
CONTINUE WITH ALGORITHM?
EVENT INTERRUPT
BLOOD PRESS. TARGET ACHIEVED?
SENSED PARAMETERS
NO
2436
END ALGORITHM
YES
2437
CARDIAC OUTPUT ACCEPTABLE?
YES
NO
2438
MODIFY RATE OF CHANGE FOR BAROREFLEX STIMULATION BASED ON CARDIAC OUTPUT

Fig. 24

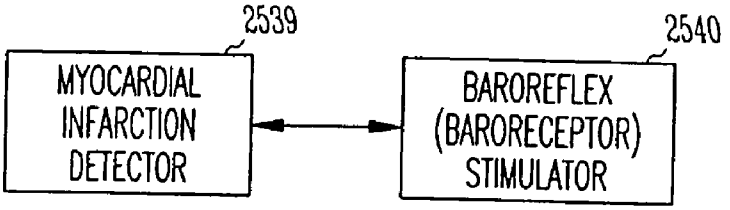


Fig. 25A

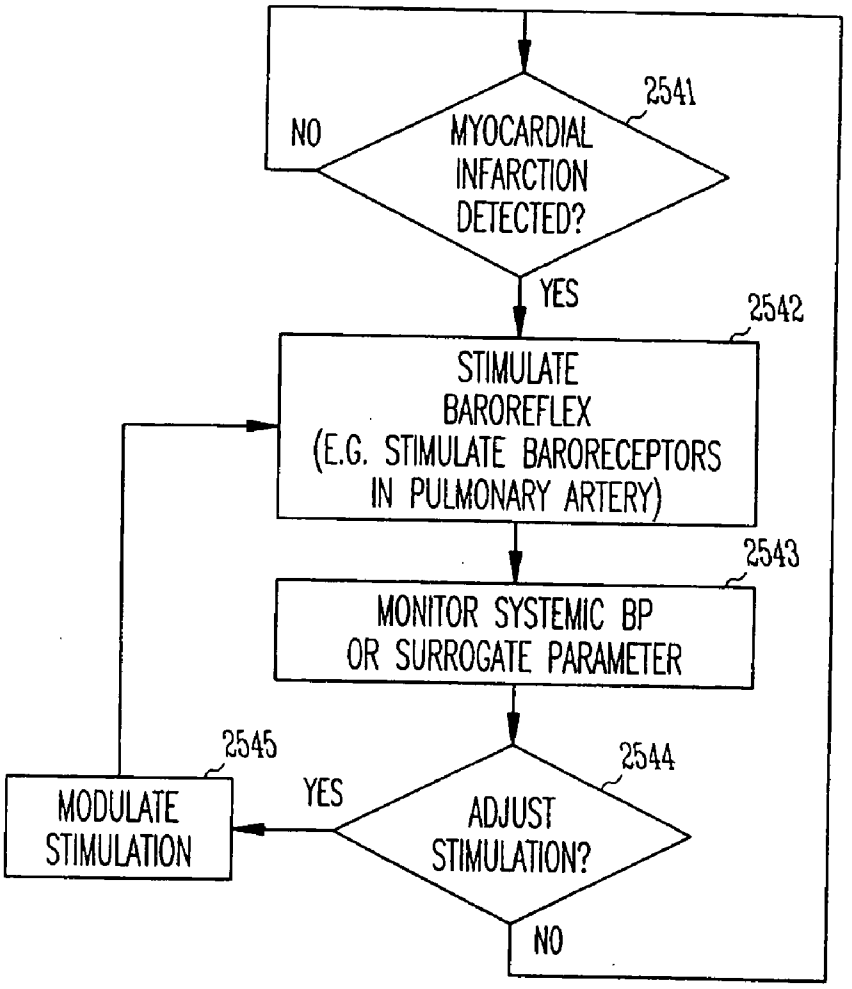


Fig. 25B

BAROREFLEX THERAPY FOR DISORDERED BREATHING

TECHNICAL FIELD

[0001] This application relates generally to implantable medical devices and, more particularly, to synchronizing baroreflex stimulation to circadian rhythm.

BACKGROUND

[0002] Implanting a chronic electrical stimulator, such as a cardiac stimulator, to deliver medical therapy(ies) is known. Examples of cardiac stimulators include implantable cardiac rhythm management (CRM) device such as pacemakers, implantable cardiac defibrillators (ICDs), and implantable devices capable of performing pacing and defibrillating functions.

[0003] CRM devices are implantable devices that provide electrical stimulation to selected chambers of the heart in order to treat disorders of cardiac rhythm. An implantable pacemaker, for example, is a CRM device that paces the heart with timed pacing pulses. If functioning properly, the pacemaker makes up for the heart's inability to pace itself at an appropriate rhythm in order to meet metabolic demand by enforcing a minimum heart rate. Some CRM devices synchronize pacing pulses delivered to different areas of the heart in order to coordinate the contractions. Coordinated contractions allow the heart to pump efficiently while providing sufficient cardiac output.

[0004] Heart failure refers to a clinical syndrome in which cardiac function causes a below normal cardiac output that can fall below a level adequate to meet the metabolic demand of peripheral tissues. Heart failure may present itself as congestive heart failure (CHF) due to the accompanying venous and pulmonary congestion. Heart failure can be due to a variety of etiologies such as ischemic heart disease.

[0005] Hypertension is a cause of heart disease and other related cardiac co-morbidities. Hypertension occurs when blood vessels constrict. As a result, the heart works harder to maintain flow at a higher blood pressure, which can contribute to heart failure. A large segment of the general population, as well as a large segment of patients implanted with pacemakers or defibrillators, suffer from hypertension. The long term mortality as well as the quality of life can be improved for this population if blood pressure and hypertension can be reduced. Many patients who suffer from hypertension do not respond to treatment, such as treatments related to lifestyle changes and hypertension drugs.

[0006] A pressoreceptive region or field is capable of sensing changes in pressure, such as changes in blood pressure. Pressoreceptor regions are referred to herein as baroreceptors, which generally include any sensors of pressure changes. For example, baroreceptors include afferent nerves and further include sensory nerve endings that are sensitive to the stretching of the wall that results from increased blood pressure from within, and function as the receptor of a central reflex mechanism that tends to reduce the pressure. Baroreflex functions as a negative feedback system, and relates to a reflex mechanism triggered by stimulation of a baroreceptor. Increased pressure stretches blood vessels, which in turn activates baroreceptors in the vessel walls. Activation of baroreceptors naturally occurs through internal pressure and stretching of the arterial wall, causing baroreflex inhibition of sympathetic nerve activity (SNA) and a reduction in systemic arterial pressure. An increase in baroreceptor activity induces a reduction of SNA, which reduces blood pressure by decreasing peripheral vascular resistance.

[0007] The general concept of stimulating afferent nerve trunks leading from baroreceptors is known. For example, direct electrical stimulation has been applied to the vagal nerve and carotid sinus. Research has indicated that electrical stimulation of the carotid sinus nerve can result in reduction of experimental hypertension, and that direct electrical stimulation to the pressoreceptive regions of the carotid sinus itself brings about reflex reduction in experimental hypertension.

[0008] Electrical systems have been proposed to treat hypertension in patients who do not otherwise respond to therapy involving lifestyle changes and hypertension drugs, and possibly to reduce drug dependency for other patients.

SUMMARY

[0009] Various aspects and embodiments of the present subject matter provide baroreflex stimulation that mimics the natural circadian rhythm by providing stimulation levels that rise and fall during the day. Such stimulation, for example, promotes sleep or rest during certain portions of the day and promotes activity during other portions of the day.

[0010] An aspect of the present subject matter relates to a baroreflex stimulator. An embodiment of the stimulator comprises a pulse generator to provide a baroreflex stimulation signal through an electrode, and a modulator to modulate the baroreflex stimulation signal based on a circadian rhythm template.

[0011] An aspect of the present subject matter relates to a baroreflex stimulator. An embodiment of the stimulator comprises a pulse generator to provide a baroreflex stimulation signal through an electrode, and means for modulating the baroreflex stimulation signal based on circadian rhythm.

[0012] An aspect of the present subject matter relates to a method for operating an implantable medical device. In an embodiment, a baroreflex stimulation therapy is applied using a baroreflex stimulator in the implantable medical device. The baroreflex stimulation therapy is modulated based on a circadian rhythm template. In one method embodiment, a circadian rhythm template is accessed, a baroreflex stimulation level is set based on the circadian rhythm template. Baroreflex stimulation is applied at the baroreflex stimulation level to a baroreceptor site in a pulmonary artery.

[0013] This Summary is an overview of some of the teachings of the present application and not intended to be an exclusive or exhaustive treatment of the present subject matter. Further details about the present subject matter are found in the detailed description and appended claims. Other aspects will be apparent to persons skilled in the art upon reading and understanding the following detailed description and viewing the drawings that form a part thereof, each of which are not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims and their equivalents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIGS. 1A and 1B** illustrate neural mechanisms for peripheral vascular control.

[0015] **FIGS. 2A-2C** illustrate a heart.

[0016] **FIG. 3** illustrates baroreceptors and afferent nerves in the area of the carotid sinuses and aortic arch.

[0017] **FIG. 4** illustrates baroreceptors in and around the pulmonary artery.

[0018] **FIG. 5** illustrates baroreceptor fields in the aortic arch, the ligamentum arteriosum and the trunk of the pulmonary artery.

[0019] **FIG. 6** illustrates a known relationship between respiration and blood pressure when the baroreflex is stimulated.

[0020] **FIG. 7** illustrates a blood pressure response to carotid nerve stimulation in a hypertensive dog during 6 months of intermittent carotid nerve stimulation.

[0021] **FIG. 8** illustrates a system including an implantable medical device (IMD) and a programmer, according to various embodiments of the present subject matter.

[0022] **FIG. 9** illustrates an implantable medical device (IMD) such as shown in the system of **FIG. 8**, according to various embodiments of the present subject matter.

[0023] **FIGS. 10A-10C** illustrate a baroreceptor stimulation lead with an integrated pressure sensor (IPS), according to various embodiments of the present subject matter.

[0024] **FIG. 11** illustrates an implantable medical device (IMD) such as shown in **FIG. 8** having a neural stimulator (NS) component and cardiac rhythm management (CRM) component, according to various embodiments of the present subject matter.

[0025] **FIG. 12** illustrates a system including a programmer, an implantable neural stimulator (NS) device and an implantable cardiac rhythm management (CRM) device, according to various embodiments of the present subject matter.

[0026] **FIG. 13** illustrates an implantable neural stimulator (NS) device such as shown in the system of **FIG. 12**, according to various embodiments of the present subject matter.

[0027] **FIG. 14** illustrates an implantable cardiac rhythm management (CRM) device such as shown in the system of **FIG. 12**, according to various embodiments of the present subject matter.

[0028] **FIG. 15** illustrates a programmer such as illustrated in the systems of **FIGS. 8 and 12** or other external device to communicate with the implantable medical device(s), according to various embodiments of the present subject matter.

[0029] **FIGS. 16A-16D** illustrate a system and methods to prevent interference between electrical stimulation from a neural stimulator (NS) device and sensing by a cardiac rhythm management (CRM) device, according to various embodiments of the present subject matter.

[0030] **FIG. 17** illustrates a system to modulate baroreflex stimulation, according to various embodiments of the present subject matter.

[0031] **FIGS. 18A-18C** illustrate methods for modulating baroreceptor stimulation based on a cardiac activity parameter, according to various embodiments of the present subject matter.

[0032] **FIGS. 19A-19B** illustrate methods for modulating baroreceptor stimulation based on a respiration parameter, according to various embodiments of the present subject matter.

[0033] **FIGS. 20A-20B** illustrate methods for modulating baroreceptor stimulation based on detection of an adverse event, according to various embodiments of the present subject matter.

[0034] **FIGS. 21A-21E** illustrate circadian rhythm.

[0035] **FIG. 22** illustrates a method for modulating baroreceptor stimulation based on circadian rhythm, according to various embodiments of the present subject matter.

[0036] **FIG. 23A**-B illustrate methods for modulating baroreceptor stimulation based on a cardiac output parameter, according to various embodiments of the present subject matter.

[0037] **FIG. 24** illustrates a method for modulating baroreceptor stimulation to reverse remodel stiffening, according to various embodiments of the present subject matter.

[0038] **FIGS. 25A-25B** illustrate a system and method to detect myocardial infarction and perform baropacing in response to the detected myocardial infarction, according to various embodiments of the present subject matter.

DETAILED DESCRIPTION

[0039] The following detailed description of the present subject matter refers to the accompanying drawings which show, by way of illustration, specific aspects and embodiments in which the present subject matter may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the present subject matter. Other embodiments may be utilized and structural, logical, and electrical changes may be made without departing from the scope of the present subject matter. References to "an", "one", or "various" embodiments in this disclosure are not necessarily to the same embodiment, and such references contemplate more than one embodiment. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope is defined only by the appended claims, along with the full scope of legal equivalents to which such claims are entitled.

Hypertension and Baroreflex Physiology

[0040] A brief discussion of hypertension and the physiology related to baroreceptors is provided to assist the reader with understanding this disclosure. This brief discussion introduces hypertension, the autonomic nervous system, and baroreflex.

[0041] Hypertension is a cause of heart disease and other related cardiac co-morbidities. Hypertension generally relates to high blood pressure, such as a transitory or

sustained elevation of systemic arterial blood pressure to a level that is likely to induce cardiovascular damage or other adverse consequences. Hypertension has been arbitrarily defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg. Hypertension occurs when blood vessels constrict. As a result, the heart works harder to maintain flow at a higher blood pressure. Consequences of uncontrolled hypertension include, but are not limited to, retinal vascular disease and stroke, left ventricular hypertrophy and failure, myocardial infarction, dissecting aneurysm, and renovascular disease.

[0042] The automatic nervous system (ANS) regulates "involuntary" organs, while the contraction of voluntary (skeletal) muscles is controlled by somatic motor nerves. Examples of involuntary organs include respiratory and digestive organs, and also include blood vessels and the heart. Often, the ANS functions in an involuntary, reflexive manner to regulate glands, to regulate muscles in the skin, eye, stomach, intestines and bladder, and to regulate cardiac muscle and the muscle around blood vessels, for example.

[0043] The ANS includes, but is not limited to, the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system is affiliated with stress and the "fight or flight response" to emergencies. Among other effects, the "fight or flight response" increases blood pressure and heart rate to increase skeletal muscle blood flow, and decreases digestion to provide the energy for "fighting or fleeing." The parasympathetic nervous system is affiliated with relaxation and the "rest and digest response" which, among other effects, decreases blood pressure and heart rate, and increases digestion to conserve energy. The ANS maintains normal internal function and works with the somatic nervous system.

[0044] The subject matter of this disclosure generally refers to the effects that the ANS has on the heart rate and blood pressure, including vasodilation and vasoconstriction. The heart rate and force is increased when the sympathetic nervous system is stimulated, and is decreased when the sympathetic nervous system is inhibited (the parasympathetic nervous system is stimulated). **FIGS. 1A and 1B** illustrate neural mechanisms for peripheral vascular control. **FIG. 1A** generally illustrates afferent nerves to vasomotor centers. An afferent nerve conveys impulses toward a nerve center. A vasomotor center relates to nerves that dilate and constrict blood vessels to control the size of the blood vessels. **FIG. 1B** generally illustrates efferent nerves from vasomotor centers. An efferent nerve conveys impulses away from a nerve center.

[0045] Stimulating the systematic and parasympathetic nervous systems can have effects other than heart rate and blood pressure. For example, stimulating the sympathetic nervous system dilates the pupil, reduces saliva and mucus production, relaxes the bronchial muscle, reduces the successive waves of involuntary contraction (peristalsis) of the stomach and the motility of the stomach, increases the conversion of glycogen to glucose by the liver, decreases urine secretion by the kidneys, and relaxes the wall and closes the sphincter of the bladder. Stimulating the parasympathetic nervous system (inhibiting the sympathetic nervous system) constricts the pupil, increases saliva and mucus production, contracts the bronchial muscle, increases secretions and motility in the stomach and large intestine, and increases digestion in the small intention, increases urine secretion, and contracts the wall and relaxes the sphincter of the bladder. The functions associated with the sympathetic and parasympathetic nervous systems are many and can be complexly integrated with each other. Thus, an indiscriminate stimulation of the sympathetic and/or parasympathetic nervous systems to achieve a desired response, such as vasodilation, in one physiological system may also result in an undesired response in other physiological systems.

[0046] Baroreflex is a reflex triggered by stimulation of a baroreceptor. A baroreceptor includes any sensor of pressure changes, such as sensory nerve endings in the wall of the auricles of the heart, cardiac fat pads, vena cava, aortic arch and carotid sinus, that is sensitive to stretching of the wall resulting from increased pressure from within, and that functions as the receptor of the central reflex mechanism that tends to reduce that pressure. Additionally, a baroreceptor includes afferent nerve trunks, such as the vagus, aortic and carotid nerves, leading from the sensory nerve endings. Stimulating baroreceptors inhibits sympathetic nerve activity (stimulates the parasympathetic nervous system) and reduces systemic arterial pressure by decreasing peripheral vascular resistance and cardiac contractility. Baroreceptors are naturally stimulated by internal pressure and the stretching of the arterial wall.

[0047] Some aspects of the present subject matter locally stimulate specific nerve endings in arterial walls rather than stimulate afferent nerve trunks in an effort to stimulate a desire response (e.g. reduced hypertension) while reducing the undesired effects of indiscriminate stimulation of the nervous system. For example, some embodiments stimulate baroreceptor sites in the pulmonary artery. Some embodiments of the present subject matter involve stimulating either baroreceptor sites or nerve endings in the aorta, the chambers of the heart, the fat pads of the heart, and some embodiments of the present subject matter involve stimulating an afferent nerve trunk, such as the vagus, carotid and aortic nerves. Some embodiments stimulate afferent nerve trunks using a cuff electrode, and some embodiments stimulate afferent nerve trunks using an intravascular lead positioned in a blood vessel proximate to the nerve, such that the electrical stimulation passes through the vessel wall to stimulate the afferent nerve trunk.

[0048] **FIGS. 2A-2C** illustrate a heart. As illustrated in **FIG. 2A**, the heart **201** includes a superior vena cava **202**, an aortic arch **203**, and a pulmonary artery **204**, and is useful to provide a contextual relationship with the illustrations in **FIGS. 3-5**. As is discussed in more detail below, the pulmonary artery **204** includes baroreceptors. A lead is capable of being intravascularly inserted through a peripheral vein and through the tricuspid valve into the right ventricle of the heart (not expressly shown in the figure) similar to a cardiac pacemaker lead, and continue from the right ventricle through the pulmonary valve into the pulmonary artery. A portion of the pulmonary artery and aorta are proximate to each other. Various embodiments stimulate baroreceptors in the aorta using a lead intravascularly positioned in the pulmonary artery. Thus, according to various aspects of the present subject matter, the baroreflex is stimulated in or around the pulmonary artery by at least one electrode intravascularly inserted into the pulmonary artery. Alternatively, a wireless stimulating device, with or without

pressure sensing capability, may be positioned via catheter into the pulmonary artery. Control of stimulation and/or energy for stimulation may be supplied by another implantable or external device via ultrasonic, electromagnetic or a combination thereof. Aspects of the present subject matter provide a relatively noninvasive surgical technique to implant a baroreceptor stimulator intravascularly into the pulmonary artery.

[0049] **FIGS. 2B-2C** illustrate the right side and left side of the heart, respectively, and further illustrate cardiac fat pads which have nerve endings that function as baroreceptor sites. **FIG. 2B** illustrates the right atrium **267**, right ventricle **268**, sinoatrial node **269**, superior vena cava **202**, inferior vena cava **270**, aorta **271**, right pulmonary veins **272**, and right pulmonary artery **273**. **FIG. 2B** also illustrates a cardiac fat pad **274** between the superior vena cava and aorta. Baroreceptor nerve endings in the cardiac fat pad **274** are stimulated in some embodiments using an electrode screwed into the fat pad, and are stimulated in some embodiments using an intravenously-fed lead proximately positioned to the fat pad in a vessel such as the right pulmonary artery or superior vena cava, for example. **FIG. 2C** illustrates the left atrium **275**, left ventricle **276**, right atrium **267**, right ventricle **268**, superior vena cava **202**, inferior vena cava **270**, aorta **271**, right pulmonary veins **272**, left pulmonary vein **277**, right pulmonary artery **273**, and coronary sinus **278**. **FIG. 2C** also illustrates a cardiac fat pad **279** located proximate to the right cardiac veins and a cardiac fat pad **280** located proximate to the inferior vena cava and left atrium. Baroreceptor nerve endings in the fat pad **279** are stimulated in some embodiments using an electrode screwed into the fat pad **279**, and are stimulated in some embodiments using an intravenously-fed lead proximately positioned to the fat pad in a vessel such as the right pulmonary artery **273** or right pulmonary vein **272**, for example. Baroreceptors in the **280** are stimulated in some embodiments using an electrode screwed into the fat pad, and are stimulated in some embodiments using an intravenously-fed lead proximately positioned to the fat pad in a vessel such as the inferior vena cava **270** or coronary sinus or a lead in the left atrium **275**, for example.

[0050] **FIG. 3** illustrates baroreceptors in the area of the carotid sinuses **305**, aortic arch **303** and pulmonary artery **304**. The aortic arch **303** and pulmonary artery **304** were previously illustrated with respect to the heart in **FIG. 2A**. As illustrated in **FIG. 3**, the vagus nerve **306** extends and provides sensory nerve endings **307** that function as baroreceptors in the aortic arch **303**, in the carotid sinus **305** and in the common carotid artery **310**. The glossopharyngeal nerve **308** provides nerve endings **309** that function as baroreceptors in the carotid sinus **305**. These nerve endings **307** and **309**, for example, are sensitive to stretching of the wall resulting from increased pressure from within. Activation of these nerve endings reduce pressure. Although not illustrated in the figures, the fat pads and the atrial and ventricular chambers of the heart also include baroreceptors. Cuffs have been placed around afferent nerve trunks, such as the vagal nerve, leading from baroreceptors to vasomotor centers to stimulate the baroreflex. According to various embodiments of the present subject matter, afferent nerve trunks can be stimulated using a cuff or intravascularly-fed lead positioned in a blood vessel proximate to the afferent nerves.

[0051] **FIG. 4** illustrates baroreceptors in and around a pulmonary artery **404**. The superior vena cava **402** and the aortic arch **403** are also illustrated. As illustrated, the pulmonary artery **404** includes a number of baroreceptors **411**, as generally indicated by the dark area. Furthermore, a cluster of closely spaced baroreceptors is situated near the attachment of the ligamentum arteriosum **412**. **FIG. 4** also illustrates the right ventricle **413** of the heart, and the pulmonary valve **414** separating the right ventricle **413** from the pulmonary artery **404**. According to various embodiments of the present subject matter, a lead is inserted through a peripheral vein and threaded through the tricuspid valve into the right ventricle, and from the right ventricle **413** through the pulmonary valve **414** and into the pulmonary artery **404** to stimulate baroreceptors in and/or around the pulmonary artery. In various embodiments, for example, the lead is positioned to stimulate the cluster of baroreceptors near the ligamentum arteriosum **412**. **FIG. 5** illustrates baroreceptor fields **511** in the aortic arch **503**, near the ligamentum arteriosum **512** and the trunk of the pulmonary artery **504**. Some embodiments position the lead in the pulmonary artery to stimulate baroreceptor sites in the aorta and/or fat pads, such as are illustrated in **FIGS. 2B-2C**.

[0052] **FIG. 6** illustrates a known relationship between respiration **615** and blood pressure **616** when the left aortic nerve is stimulated. When the nerve is stimulated at **617**, the blood pressure **616** drops, and the respiration **615** becomes faster and deeper, as illustrated by the higher frequency and amplitude of the respiration waveform. The respiration and blood pressure appear to return to the pre-stimulated state in approximately one to two minutes after the stimulation is removed. Various embodiments of the present subject matter use this relationship between respiration and blood pressure by using respiration as a surrogate parameter for blood pressure.

[0053] **FIG. 7** illustrates a known blood pressure response to carotid nerve stimulation in a hypertensive dog during 6 months of intermittent carotid nerve stimulation. The figure illustrates that the blood pressure of a stimulated dog **718** is significantly less than the blood pressure of a control dog **719** that also has high blood pressure. Thus, intermittent stimulation is capable of triggering the baroreflex to reduce high blood pressure.

Baroreflex Stimulator Systems

[0054] Various embodiments of the present subject matter relate to baroreflex stimulator systems. Such baroreflex stimulation systems are also referred to herein as neural stimulator (NS) devices or components. Examples of neural stimulators include anti-hypertension (AHT) devices or AHT components that are used to treat hypertension. Various embodiments of the present subject matter include stand-alone implantable baroreceptor stimulator systems, include implantable devices that have integrated NS and cardiac rhythm management (CRM) components, and include systems with at least one implantable NS device and an implantable CRM device capable of communicating with each other either wirelessly or through a wire lead connecting the implantable devices. Integrating NS and CRM functions that are either performed in the same or separate devices improves aspects of the NS therapy and cardiac therapy by allowing these therapies to work together intelligently.

[0055] **FIG. 8** illustrates a system **820** including an implantable medical device (IMD) **821** and a programmer **822**, according to various embodiments of the present subject matter. Various embodiments of the IMD **821** include neural stimulator functions only, and various embodiments include a combination of NS and CRM functions. Some embodiments of the neural stimulator provide AHT functions. The programmer **822** and the IMD **821** are capable of wirelessly communicating data and instructions. In various embodiments, for example, the programmer **822** and IMD **821** use telemetry coils to wirelessly communicate data and instructions. Thus, the programmer can be used to adjust the programmed therapy provided by the IMD **821**, and the IMD can report device data (such as battery and lead resistance) and therapy data (such as sense and stimulation data) to the programmer using radio telemetry, for example. According to various embodiments, the IMD **821** stimulates baroreceptors to provide NS therapy such as AHT therapy. Various embodiments of the IMD **821** stimulate baroreceptors in the pulmonary artery using a lead fed through the right ventricle similar to a cardiac pacemaker lead, and further fed into the pulmonary artery. According to various embodiments, the IMD **821** includes a sensor to sense ANS activity. Such a sensor can be used to perform feedback in a closed loop control system. For example, various embodiments sense surrogate parameters, such as respiration and blood pressure, indicative of ANS activity. According to various embodiments, the IMD further includes cardiac stimulation capabilities, such as pacing and defibrillating capabilities in addition to the capabilities to stimulate baroreceptors and/or sense ANS activity.

[0056] **FIG. 9** illustrates an implantable medical device (IMD) **921** such as the IMD **821** shown in the system **820** of **FIG. 8**, according to various embodiments of the present subject matter. The illustrated IMD **921** performs NS functions. Some embodiments of the illustrated IMD **921** performs an AHT function, and thus illustrates an implantable AHT device. The illustrated device **921** includes controller circuitry **923** and a memory **924**. The controller circuitry **923** is capable of being implemented using hardware, software, and combinations of hardware and software. For example, according to various embodiments, the controller circuitry **923** includes a processor to perform instructions embedded in the memory **924** to perform functions associated with NS therapy such as AHT therapy. For example, the illustrated device **921** further includes a transceiver **925** and associated circuitry for use to communicate with a programmer or another external or internal device. Various embodiments have wireless communication capabilities. For example, some transceiver embodiments use a telemetry coil to wirelessly communicate with a programmer or another external or internal device.

[0057] The illustrated device **921** further includes baroreceptor stimulation circuitry **926**. Various embodiments of the device **921** also includes sensor circuitry **927**. One or more leads are able to be connected to the sensor circuitry **927** and baroreceptor stimulation circuitry **926**. The baroreceptor stimulation circuitry **926** is used to apply electrical stimulation pulses to desired baroreceptors sites, such as baroreceptor sites in the pulmonary artery, through one or more stimulation electrodes. The sensor circuitry **927** is used to detect and process ANS nerve activity and/or surrogate parameters such as blood pressure, respiration and the like, to determine the ANS activity.

[0058] According to various embodiments, the stimulator circuitry **926** includes modules to set any one or any combination of two or more of the following pulse features: the amplitude **928** of the stimulation pulse, the frequency **929** of the stimulation pulse, the burst frequency **930** or duty cycle of the pulse, and the wave morphology **931** of the pulse. Examples of wave morphology include a square wave, triangle wave, sinusoidal wave, and waves with desired harmonic components to mimic white noise such as is indicative of naturally-occurring baroreflex stimulation.

[0059] **FIGS. 10A-10C** illustrate a baroreceptor stimulation lead with an integrated pressure sensor (IPS), according to various embodiments of the present subject matter. Although not drawn to scale, these illustrated leads **1032**A, **1032**B and **1032**C include an IPS **1033** with a baroreceptor stimulator electrode **1034** to monitor changes in blood pressure, and thus the effect of the baroreceptor stimulation. These lead illustrations should not be read as limiting other aspects and embodiments of the present subject matter. In various embodiments, for example, micro-electrical mechanical systems (MEMS) technology is used to sense the blood pressure. Some sensor embodiments determine blood pressure based on a displacement of a membrane.

[0060] **FIGS. 10A-10C** illustrate an IPS on a lead. Some embodiments implant an IPS in an IMD or NS device. The stimulator and sensor functions can be integrated, even if the stimulator and sensors are located in separate leads or positions.

[0061] The lead **1032**A illustrated in **FIG. 10A** includes a distally-positioned baroreceptor stimulator electrode **1034** and an IPS **1033**. This lead, for example, is capable of being intravascularly introduced to stimulate a baroreceptor site, such as the baroreceptor sites in the pulmonary artery, aortic arch, ligamentum arteriosum, the coronary sinus, in the atrial and ventricular chambers, and/or in cardiac fat pads.

[0062] The lead **1032**B illustrated in **FIG. 10B** includes a tip electrode **1035**, a first ring electrode **1036**, second ring electrode **1034**, and an IPS **1033**. This lead may be intravascularly inserted into or proximate to chambers of the heart and further positioned proximate to baroreceptor sites such that at least some of the electrodes **1035**, **1036** and **1034** are capable of being used to pace or otherwise stimulate the heart, and at least some of the electrodes are capable of stimulating at least one baroreceptor site. The IPS **1033** is used to sense the blood pressure. In various embodiments, the IPS is used to sense the blood pressure in the vessel proximate to the baroreceptor site selected for stimulation.

[0063] The lead **1032**C illustrated in **FIG. 10C** includes a distally-positioned baroreceptor stimulator electrode **1034**, an IPS **1033** and a ring electrode **1036**. This lead **1032**C may, for example, be intravascularly inserted into the right atrium and ventricle, and then through the pulmonary valve into the pulmonary artery. Depending on programming in the device, the electrode **1036** can be used to pace and/or sense cardiac activity, such as that which may occur within the right ventricle, and the electrode **1034** and IPS **1033** are located near baroreceptors in or near the pulmonary artery to stimulate and sense, either directly or indirectly through surrogate parameters, baroreflex activity.

[0064] Thus, various embodiments of the present subject matter provide an implantable NS device that automatically

modulates baroreceptor stimulation using an IPS. Integrating the pressure sensor into the lead provides localized feedback for the stimulation. This localized sensing improves feedback control. For example, the integrated sensor can be used to compensate for inertia of the baroreflex such that the target is not continuously overshot. According to various embodiments, the device monitors pressure parameters such as mean arterial pressure, systolic pressure, diastolic pressure and the like. As mean arterial pressure increases or remains above a programmable target pressure, for example, the device stimulates baroreceptors at an increased rate to reduce blood pressure and control hypertension. As mean arterial pressure decreases towards the target pressure, the device responds by reducing baroreceptor stimulation. In various embodiments, the algorithm takes into account the current metabolic state (cardiac demand) and adjusts neural stimulation accordingly. A NS device having an IPS is able to automatically modulate baroreceptor stimulation, which allows an implantable NS device to determine the level of hypertension in the patient and respond by delivering the appropriate level of therapy. However, it is noted that other sensors, including sensors that do not reside in an NS or neural stimulator device, can be used to provide close loop feedback control.

[0065] **FIG. 11** illustrates an implantable medical device (IMD) **1121** such as shown at **821** in **FIG. 8** having an anti-hypertension (AHT) component **1137** and cardiac rhythm management (CRM) component **1138**, according to various embodiments of the present subject matter. The illustrated device **1121** includes a controller **1123** and a memory **1124**. According to various embodiments, the controller **1123** includes hardware, software, or a combination of hardware and software to perform the baroreceptor stimulation and CRM functions. For example, the programmed therapy applications discussed in this disclosure are capable of being stored as computer-readable instructions embodied in memory and executed by a processor. According to various embodiments, the controller **1123** includes a processor to execute instructions embedded in memory to perform the baroreceptor stimulation and CRM functions. The illustrated device **1121** further includes a transceiver and associated circuitry for use to communicate with a programmer or another external or internal device. Various embodiments include a telemetry coil.

[0066] The CRM therapy section **1138** includes components, under the control of the controller, to stimulate a heart and/or sense cardiac signals using one or more electrodes. The CRM therapy section includes a pulse generator **1139** for use to provide an electrical signal through an electrode to stimulate a heart, and further includes sense circuitry **1140** to detect and process sensed cardiac signals. An interface **1141** is generally illustrated for use to communicate between the controller **1123** and the pulse generator **1139** and sense circuitry **1140**. Three electrodes are illustrated as an example for use to provide CRM therapy. However, the present subject matter is not limited to a particular number of electrode sites. Each electrode may include its own pulse generator and sense circuitry. However, the present subject matter is not so limited. The pulse generating and sensing functions can be multiplexed to function with multiple electrodes.

[0067] The NS therapy section **1137** includes components, under the control of the controller, to stimulate a baroreceptor and/or sense ANS parameters associated with nerve activity or surrogates of ANS parameters such as blood pressure and respiration. Three interfaces **1142** are illustrated for use to provide ANS therapy. However, the present subject matter is not limited to a particular number interfaces, or to any particular stimulating or sensing functions. Pulse generators **1143** are used to provide electrical pulses to an electrode for use to stimulate a baroreceptor site. According to various embodiments, the pulse generator includes circuitry to set, and in some embodiments change, the amplitude of the stimulation pulse, the frequency of the stimulation pulse, the burst frequency of the pulse, and the morphology of the pulse such as a square wave, triangle wave, sinusoidal wave, and waves with desired harmonic components to mimic white noise or other signals. Sense circuits **1144** are used to detect and process signals from a sensor, such as a sensor of nerve activity, blood pressure, respiration, and the like. The interfaces **1142** are generally illustrated for use to communicate between the controller **1123** and the pulse generator **1143** and sense circuitry **1144**. Each interface, for example, may be used to control a separate lead. Various embodiments of the NS therapy section only include a pulse generator to stimulate baroreceptors. For example, the NS therapy section provides AHT therapy.

[0068] An aspect of the present subject matter relates to a chronically-implanted stimulation system specially designed to treat hypertension by monitoring blood pressure and stimulating baroreceptors to activate the baroreceptor reflex and inhibit sympathetic discharge from the vasomotor center. Baroreceptors are located in various anatomical locations such as the carotid sinus and the aortic arch. Other baroreceptor locations include the pulmonary artery, including the ligamentum arteriosum, and sites in the atrial and ventricular chambers. In various embodiments, the system is integrated into a pacemaker/defibrillator or other electrical stimulator system. Components of the system include a high-frequency pulse generator, sensors to monitor blood pressure or other pertinent physiological parameters, leads to apply electrical stimulation to baroreceptors, algorithms to determine the appropriate time to administer stimulation, and algorithms to manipulate data for display and patient management.

[0069] Various embodiments relate to a system that seeks to deliver electrically mediated NS therapy, such as AHT therapy, to patients. Various embodiments combine a "stand-alone" pulse generator with a minimally invasive, unipolar lead that directly stimulates baroreceptors in the vicinity of the heart, such as in the pulmonary artery. This embodiment is such that general medical practitioners lacking the skills of specialist can implant it. Various embodiments incorporate a simple implanted system that can sense parameters indicative of blood pressure. This system adjusts the therapeutic output (waveform amplitude, frequency, etc.) so as to maintain a desired quality of life. In various embodiments, an implanted system includes a pulse generating device and lead system, the stimulating electrode of which is positioned near endocardial baroreceptor tissues using transvenous implant technique(s). Another embodiment includes a system that combines NS therapy with traditional bradyarrhythmia, tachyarrhythmia, and/or congestive heart failure (CHF) therapies. Some embodiments use an additional "baroreceptor lead" that emerges from the device header and is paced from a modified traditional pulse generating system. In

another embodiment, a traditional CRM lead is modified to incorporate proximal electrodes that are naturally positioned near baroreceptor sites. With these leads, distal electrodes provide CRM therapy and proximate electrodes stimulate baroreceptors.

[0070] A system according to these embodiments can be used to augment partially successful treatment strategies. As an example, undesired side effects may limit the use of some pharmaceutical agents. The combination of a system according to these embodiments with reduced drug doses may be particularly beneficial.

[0071] According to various embodiments, the lead(s) and the electrode(s) on the leads are physically arranged with respect to the heart in a fashion that enables the electrodes to properly transmit pulses and sense signals from the heart, and with respect to baroreceptors to stimulate the baroreflex. As there may be a number of leads and a number of electrodes per lead, the configuration can be programmed to use a particular electrode or electrodes. According to various embodiments, the baroreflex is stimulated by stimulating afferent nerve trunks.

[0072] **FIG. 12** illustrates a system **1220** including a programmer **1222**, an implantable neural stimulator (NS) device **1237** and an implantable cardiac rhythm management (CRM) device **1238**, according to various embodiments of the present subject matter. Various aspects involve a method for communicating between an NS device **1237**, such as an AHT device, and a CRM device **1238** or other cardiac stimulator. In various embodiments, this communication allows one of the devices **1237** or **1238** to deliver more appropriate therapy (i.e. more appropriate NS therapy or CRM therapy) based on data received from the other device. Some embodiments provide on-demand communications. In various embodiments, this communication allows each of the devices **1237** and **1238** to deliver more appropriate therapy (i.e. more appropriate NS therapy and CRM therapy) based on data received from the other device. The illustrated NS device **1237** and the CRM device **1238** are capable of wirelessly communicating with each other, and the programmer is capable of wirelessly communicating with at least one of the NS and the CRM devices **1237** and **1238**. For example, various embodiments use telemetry coils to wirelessly communicate data and instructions to each other. In other embodiments, communication of data and/or energy is by ultrasonic means.

[0073] In some embodiments, the NS device **1237** stimulates the baroreflex to provide NS therapy, and senses ANS activity directly or using surrogate parameters, such as respiration and blood pressure, indicative of ANS activity. The CRM device **1238** includes cardiac stimulation capabilities, such as pacing and defibrillating capabilities. Rather than providing wireless communication between the NS and CRM devices **1237** and **1238**, various embodiments provide a communication cable or wire, such as an intravenously-fed lead, for use to communicate between the NS device **1237** and the CRM device **1238**.

[0074] **FIG. 13** illustrates an implantable neural stimulator (NS) device **1337** such as shown at **1237** in the system of **FIG. 12**, according to various embodiments of the present subject matter. **FIG. 14** illustrates an implantable cardiac rhythm management (CRM) device **1438** such as shown at **1238** in the system of **FIG. 12**, according to various embodiments of the present subject matter. Functions of the components for the NS device **1337** were previously discussed with respect to **FIGS. 9 and 11** (the NS component **1137**), and functions of the components for the CRM device **1238** were previously discussed with respect to **FIG. 11** (the CRM component **1138**). In the interest of brevity, these discussions with respect to the NS and CRM functions are not repeated here. Various embodiments of the NS and CRM devices include wireless transceivers **1325** and **1425**, respectively, to wirelessly communicate with each other. Various embodiments of the NS and CRM devices include a telemetry coil or ultrasonic transducer to wirelessly communicate with each other.

[0075] According to various embodiments, for example, the NS device is equipped with a telemetry coil, allowing data to be exchanged between it and the CRM device, allowing the NS device to modify therapy based on electrophysiological parameters such as heart rate, minute ventilation, atrial activation, ventricular activation, and cardiac events. In addition, the CRM device modifies therapy based on data received from the NS device, such as mean arterial pressure, systolic and diastolic pressure, and baroreceptors stimulation rate.

[0076] Some NS device embodiments are able to be implanted in patients with existing CRM devices, such that the functionality of the NS device is enhanced by receiving physiological data that is acquired by the CRM device. The functionality of two or more implanted devices is enhanced by providing communication capabilities between or among the implanted devices. In various embodiments, the functionality is further enhanced by designing the devices to wirelessly communicate with each other.

[0077] **FIG. 15** illustrates a programmer **1522**, such as the programmer **822** and **1222** illustrated in the systems of **FIGS. 8 and 12**, or other external device to communicate with the implantable medical device(s) **1237** and/or **1238**, according to various embodiments of the present subject matter. An example of another external device includes Personal Digital Assistants (PDAs) or personal laptop and desktop computers in an Advanced Patient Management (APM) system. The illustrated device **1522** includes controller circuitry **1545** and a memory **1546**. The controller circuitry **1545** is capable of being implemented using hardware, software, and combinations of hardware and software. For example, according to various embodiments, the controller circuitry **1545** includes a processor to perform instructions embedded in the memory **1546** to perform a number of functions, including communicating data and/or programming instructions to the implantable devices. The illustrated device **1522** further includes a transceiver **1547** and associated circuitry for use to communicate with an implantable device. Various embodiments have wireless communication capabilities. For example, various embodiments of the transceiver **1547** and associated circuitry include a telemetry coil for use to wirelessly communicate with an implantable device. The illustrated device **1522** further includes a display **1548**, input/output (I/O) devices **1549** such as a keyboard or mouse/pointer, and a communications interface **1550** for use to communicate with other devices, such as over a communication network.

Programmed Therapy Applications

[0078] NS and/or CRM functions of a system, whether implemented in two separate and distinct implantable

devices or integrated as components into one implantable device, includes processes for performing NS and/or CRM therapy or portions of the therapy. In some embodiments, the NS therapy provides AHT therapy. These processes can be performed by a processor executing computer-readable instructions embedded in memory, for example. These therapies include a number of applications, which have various processes and functions, some of which are identified and discussed below. The processes and functions of these therapies are not necessarily mutually exclusive, as some embodiments of the present subject matter include combinations of two or more of the below-identified processes and functions.

[0079] Accounting for Neural Stimulation to Accurately Sense Signals

[0080] **FIGS. 16A-16D** illustrate a system and methods to prevent interference between electrical stimulation from an neural stimulator (NS) device and sensing by a cardiac rhythm management (CRM) device, according to various embodiments of the present subject matter. Neural stimulation is accounted for to improve the ability to sense signals, and thus reduce or eliminate false positives associated with detecting a cardiac event. The NS device includes an AHT device in some embodiments. For example, the NS device communicates with and prevents or otherwise compensates for baroreflex stimulation such that the CRM device does not unintentionally react to the baroreflex stimulation, according to some embodiments. Some embodiments automatically synchronize the baroreflex stimulation with an appropriate refraction in the heart. For example, some systems automatically synchronize stimulation of baroreceptors in or around the pulmonary artery with atrial activation. Thus, the functions of the CRM device are not adversely affected by detecting far-field noise generated by the baroreflex stimulation, even when the baroreflex stimulations are generated near the heart and the CRM sensors that detect the cardiac electrical activation.

[0081] **FIG. 16A** generally illustrates a system **1654** that includes NS functions **1651** (such as may be performed by a NS device or a NS component in an integrated NS/CRM device), CRM functions **1652** (such as may be performed by a CRM device or a CRM component in an integrated NS/CRM device) and capabilities to communicate **1653** between the NS and CRM functions. The illustrated communication is bidirectional wireless communication. However, the present subject matter also contemplates unidirectional communication, and further contemplates wired communication. Additionally, the present subject matter contemplates that the NS and CRM functions **1651** and **1652** can be integrated into a single implantable device such that the communication signal is sent and received in the device, or in separate implantable devices. Although baroreflex stimulation as part of neural stimulation is specifically discussed, this aspect of the present subject matter is also applicable to prevent, or account or other wise compensate for, unintentional interference detectable by a sensor and generated from other electrical stimulators.

[0082] **FIG. 16B** illustrates a process where CRM functions do not unintentionally react to baroreflex stimulation, according to various embodiments. **FIG. 16B** illustrates a process where the NS device or component **1651** sends an alert or otherwise informs the CRM device or component when baroreceptors are being electrically stimulated. In the illustrated embodiment, the NS device/component determines at **1655** if electrical stimulation, such as baroreflex stimulation, is to be applied. When electrical stimulation is to be applied, the NS device or component **1651** sends at **1656** an alert **1657** or otherwise informs the CRM device or component **1652** of the electrical stimulation. At **1658**, the electrical stimulation is applied by the NS device/component. At **1659** CRM therapy, including sensing, is performed. At **1660**, the CRM device/component determines whether an alert **1657** has been received from the NS device/component. If an alert has been received, an event detection algorithm is modified at **1661** to raise a detection threshold, provide a blackout or blanking window, or otherwise prevent the electrical stimulation in the NS device or component from being misinterpreted as an event by the CRM device/component.

[0083] **FIG. 16C** illustrates a process where CRM functions do not unintentionally react to baroreflex stimulation, according to various embodiments. The CRM device/component **1652** determines a refractory period for the heart at **1662**. At **1663**, if a refractory period is occurring or is expected to occur in a predictable amount of time, an enable **1664** corresponding to the refractory is provided to the NS device/component **1651**. The AHT device/component **1651** determines if electrical stimulation is desired at **1665**. When desired, the AHT device/component applies electrical stimulation during a refractory period at **1666**, as controlled by the enable signal **1664**. **FIG. 16D** illustrates a refractory period at **1667** in a heart and a baroreflex stimulation **1668**, and further illustrates that baroreflex stimulation is applied during the refractory period.

[0084] A refractory period includes both absolute and relative refractory periods. Cardiac tissue is not capable of being stimulated during the absolute refractory period. The required stimulation threshold during an absolute refractory period is basically infinite. The relative refractory period occurs after the absolute refractory period. During the relative refractory period, as the cardiac tissue begins to repolarize, the stimulation threshold is initially very high and drops to a normal stimulation threshold by the end of the relative refractory period. Thus, according to various embodiments, a neural stimulator applies neural stimulation during either the absolute refractory period or during a portion of the relative refractory period corresponding a sufficiently high stimulation threshold to prevent the neural stimulation from capturing cardiac tissue.

[0085] Various embodiments of the present subject matter relate to a method of sensing atrial activation and confining pulmonary artery stimulation to the atrial refractory period, preventing unintentional stimulation of nearby atrial tissue. An implantable baroreceptor stimulation device monitors atrial activation with an atrial sensing lead. A lead in the pulmonary artery stimulates baroreceptors in the vessel wall. However, instead of stimulating these baroreceptors continuously, the stimulation of baroreceptors in the pulmonary artery occurs during the atrial refractory period to avoid capturing nearby atrial myocardium, maintaining the intrinsic atrial rate and activation. Various embodiments of the present subject matter combine an implantable device for stimulating baroreceptors in the wall of the pulmonary artery with the capability for atrial sensing. Various embodiments

stimulate baroreceptors in the cardiac fat pads, in the heart chambers, and/or afferent nerves.

[0086] **FIG. 17** illustrates a system **1769** to modulate baroreflex stimulation, according to various embodiments of the present subject matter. The illustrated system **1769** includes a baroreflex stimulator **1751**, such as stimulator to stimulate baroreceptors in and around the pulmonary artery. The baroreflex stimulator can be included in a stand-alone NS device or as a NS component in an integrated NS/CRM device, for example. The illustrated stimulator **1751** includes a modulator **1769** for use to selectively increase and decrease the applied baroreflex stimulation. According to various embodiments, the modulator **1769** includes any one of the following modules: a module **1770** to change the amplitude of the stimulation pulse; a module **1771** to change the frequency of the stimulation pulse; and a module **1772** to change the burst frequency of the stimulation pulse. The burst frequency can also be referred to as a duty cycle. According to various embodiments, the modulator **1769** includes functions for the various combinations of two or more of the modules **1770**, **1771** and **1772**. Additionally, a stimulator can include a waveform generator capable of providing different waveforms in response to a control signal.

[0087] Various embodiments of the system include any one or any combination of a cardiac activity monitor **1773**, an adverse event detector **1774**, a respiration monitor **1775**, and a circadian rhythm template **1776** which are capable of controlling the modulator **1769** of the stimulator **1759** to appropriately apply a desired level of baroreflex stimulation. Each of these **1773**, **1774**, **1775**, and **1776** are associated with a method to modulate a baroreflex signal. According to various embodiments, the system includes means to modulate a baroreflex signal based on the following parameters or parameter combinations: cardiac activity (**1773**); an adverse event (**1774**); respiration (**1775**); circadian rhythm (**1776**); cardiac activity (**1773**) and an adverse event (**1774**); cardiac activity (**1773**) and respiration (**1775**); cardiac activity (**1773**) and circadian rhythm (**1776**); an adverse event (**1774**) and respiration (**1775**); an adverse event (**1774**) and circadian rhythm (**1776**); respiration (**1775**) and circadian rhythm (**1776**); cardiac activity (**1773**), an adverse event (**1774**), and respiration (**1775**); cardiac activity (**1773**), an adverse event (**1774**), and circadian rhythm (**1776**); cardiac activity (**1773**), respiration (**1775**), and circadian rhythm (**1776**); an adverse event (**1774**), respiration (**1775**) and circadian rhythm (**1776**); and cardiac activity (**1773**), an adverse event (**1774**), respiration (**1775**) and circadian rhythm (**1776**).

[0088] The stimulation can be applied to an afferent nerve trunk such as the vagal nerve using a cuff electrode or an intravascularly-fed lead positioned proximate to the nerve trunk. The stimulation can be applied to baroreceptor sites such are located in the pulmonary artery, aortic arch, and carotid sinus, for example, using intravenously-fed leads. The stimulation can be applied to baroreceptor sites located in cardiac fat pads using intravenously-fed leads or by screwing electrodes into the fat pads. Embodiments of the cardiac activity detector **1774**, for example, include any one or any combination of a heart rate monitor **1777**, a minute ventilation monitor **1778**, and an acceleration monitor **1779**. The respiration monitor **1775** functions as a surrogate for monitoring blood pressure. Embodiments of the respiration monitor **1775** include any one or any combination of a tidal volume monitor **1780** and a minute ventilation module **1781**. Embodiments of the circadian rhythm template **1776** include any one or combination of a custom generated template **1782** and a preprogrammed template **1783**. These embodiments are discussed in more detail below with respect to **FIGS. 18A-18C**, **19A-19B**, **20A-20B**, **21A-21E**, **22** and **23A-23C**.

[0089] Various embodiments use the circadian rhythm template to provide AHT therapy. Various embodiments use the circadian rhythm template to provide apnea therapy.

[0090] Modulation of Baroreflex Stimulation Based on Systolic Intervals

[0091] Activation of the sympathetic or parasympathetic nervous systems is known to alter certain systolic intervals, primarily the pre-ejection period (PEP), the time interval between sensed electrical activity within the ventricle (e.g. sensing of the "R" wave) and the onset of ventricular ejection of blood. The PEP may be measured from the sensed electrical event to the beginning of pressure increase in the pulmonary artery, using a pulmonary arterial pressure sensor, or may be measured to the beginning of an increase in intracardiac impedance, accompanying a decrease in ventricular volume during ejection, using electrodes positioned in the right or spanning the left ventricle. At rest, as determined by heart rate or body activity measured with an accelerometer for example, neural stimulation is modulated to maintain PEP in a pre-programmed range. A sudden decrease in PEP indicates an increase in sympathetic tone associated with exercise or emotional stress. This condition may be used to decrease neural stimulation permitting increases in heart rate and contractility necessary to meet metabolic demand. In like manner, a subsequent dramatic lengthening of PEP marks the end of increased metabolic demand. At this time control of blood pressure with neural stimulation could recommence.

[0092] Modulation of Baroreflex Stimulation Based on Cardiac Activity

[0093] The present subject matter describes a method of automatically modulating baroreceptor stimulation based on cardiac activity, such as can be determined by the heart rate, minute ventilation, acceleration and combinations thereof. The functionality of a device for electrically stimulating baroreceptors is enhanced by applying at least a relatively high baropacing rate during rest when metabolic demand is relatively low, and progressively less baropacing during physical exertion as metabolic demand increases. Indices of cardiac activity are used to automatically modulate the electrical stimulation of baroreceptors, allowing an implantable anti-hypertension device to respond to changes in metabolic demand. According to various embodiments, a CRM device, such as a pacemaker, AICD or CRT devices, also has a baroreceptor stimulation lead. The device monitors cardiac activity through existing methods using, for example, a blended sensor. A blended sensor includes two sensors to measure parameters such as acceleration and minute ventilation. The output of the blended sensor represents a composite parameter. Various NS and AHT therapies use composite parameters derived from two or more sensed parameters as discussed within this disclosure. At rest (lower cardiac activity) the device stimulates baroreceptors at a higher rate, reducing blood pressure and controlling hyper-

tension. As cardiac activity increases, the device responds by temporarily reducing baroreceptor stimulation. This results in a temporary increase in blood pressure and cardiac output, allowing the body to respond to increased metabolic demand. For example, some embodiments provide baroreflex stimulation during rest and withdraw baroreflex stimulation during exercise to match normal blood pressure response to exercise. A pressure transducer can be used to determine activity. Furthermore, activity can be sensed using sensors that are or have been used to drive rate adaptive pacing. Examples of such sensors include sensor to detect body movement, heart rate, QT interval, respiration rate, transthoracic impedance, tidal volume, minute ventilation, body posture, electroencephalogram (EEG), electrocardiogram (ECG), electrooculogram (EOG), electromyogram (EMG), muscle tone, body temperature, pulse oximetry, time of day and pre-ejection interval from intracardiac impedance.

[0094] Various embodiments of the cardiac activity monitor includes a sensor to detect at least one pressure parameter such as a mean arterial parameter, a pulse pressure determined by the difference between the systolic and diastolic pressures, end systolic pressure (pressure at the end of the systole), and end diastolic pressure (pressure at the end of the diastole). Various embodiments of the cardiac activity monitor include a stroke volume monitor. Heart rate and pressure can be used to derive stroke volume. Various embodiments of the cardiac activity monitor use at least one electrogram measurement to determine cardiac activity. Examples of such electrogram measurements include the R-R interval, the P-R interval, and the QT interval. Various embodiments of the cardiac activity monitor use at least one electrocardiogram (ECG) measurement to determine cardiac activity.

[0095] **FIGS. 18A-18C** illustrate methods for modulating baroreceptor stimulation based on a cardiac activity parameter, according to various embodiments of the present subject matter. The cardiac activity can be determined by a CRM device, an NS device, or an implantable device with NS/CRM capabilities. A first process **1884**A for modulating baroreceptor stimulation based on cardiac activity is illustrated in **FIG. 18A**. At **1885**A the activity level is determined. According to various embodiments, the determination of activity level is based on heart rate, minute ventilation, acceleration or any combination of heart rate, minute ventilation, acceleration. In the illustrated process, the activity level has two defined binary levels (e.g. HI and LO). In some embodiments, the LO level includes no stimulation. It is determined whether the activity level is HI or LO. At **1886**A, the baroreceptor stimulation level is set based on the determined activity level. A LO stimulation level is set if the activity level is determined to be HI, and a HI stimulation level is set if the activity level is determined to be LO.

[0096] A second process **1884**B for modulating baroreceptor stimulation based on cardiac activity is illustrated in **FIG. 18B**. At **1885**B the activity level is determined. According to various embodiments, the determination of activity level is based on heart rate, minute ventilation, acceleration or any combination of heart rate, minute ventilation, acceleration. In the illustrated process, the activity level has more than two defined levels or n defined levels. It is determined whether the activity level is level 1, level 2 . . . or level n. The activity level labels correspond to an increasing activity. At **1886**B, the baroreceptor stimulation level is set based on the determined activity level. Available stimulation levels include level n . . . level 2 and level 1, where the stimulation level labels correspond to increasing stimulation. According to various embodiments, the selected baroreceptor stimulation level is inversely related to the determined activity level. For example, if it is determined that the cardiac activity level is at the highest level n, then the stimulation level is set to the lowest level n. If it determined that the stimulation level is at the first or second to the lowest level, level 1 or level 2 respectively, then the stimulation level is set to the first or second to the highest level, level 1 or level 2 respectively.

[0097] Another process **1884**C for modulating baroreceptor stimulation based on cardiac activity is illustrated in **FIG. 18C**. At **1887**, an acquired cardiac activity parameter is compared to a target activity parameter. If the acquired cardiac activity is lower than the target activity parameter, baroreceptor stimulation is increased at **1888**. If the acquired cardiac activity is higher than the target activity parameter, baroreceptor stimulation is decreased at **1889**.

[0098] An aspect of the present subject matter relates to a method of automatically modulating the intensity of baroreceptor stimulation based on respiration, as determined by tidal volume or minute ventilation. Instead of applying continuous baroreceptor stimulation, the NS device monitors the level of hypertension and delivers an appropriate level of therapy, using respiration as a surrogate for blood pressure, allowing the device to modulate the level of therapy. The present subject matter uses indices of respiration, such as impedance, to determined tidal volume and minute ventilation and to automatically modulate baroreceptor stimulation. Thus, an implantable NS device is capable of determining the level of hypertension in the patient and respond by delivering an appropriate level of therapy. In various embodiments, an implantable NS device contains a sensor to measure tidal volume or minute ventilation. For example, various embodiments measure transthoracic impedance to obtain a rate of respiration. The device receives this data from a CRM device in some embodiments. The NS device periodically monitors these respiration parameters. As respiration decreases or remains below a programmable target, the device stimulates baroreceptors at an increased rate, reducing blood pressure and controlling hypertension. As mean arterial pressure increases towards the target, the device responds by reducing baroreceptor stimulation. In this way, the AHT device continuously delivers an appropriate level of therapy.

[0099] **FIGS. 19A-19B** illustrate methods for modulating baroreceptor stimulation based on a respiration parameter, according to various embodiments of the present subject matter. The respiration parameter can be determined by a CRM device, an NS device, or an implantable device with NS/CRM capabilities. One embodiment of a method for modulating baroreceptor stimulation based on a respiration parameter is illustrated at **1910**A in **FIG. 19A**. The respiration level is determined at **1911**, and the baroreceptor stimulation level is set at **1912** based on the determined respiration level. According to various embodiments, the desired baropacing level is tuned at **1913**. For example, one embodiment compares an acquired parameter to a target parameter at **1914**. The baropacing can be increased at **1915**

or decreased at **1916** based on the comparison of the acquired parameter to the target parameter.

[**0100**] One embodiment of a method for modulating baroreceptor stimulation based on a respiration parameter is illustrated at **1910**B in **FIG. 19B**. At **1916**, a baroreflex event trigger occurs, which triggers an algorithm for a baroreflex stimulation process. At **1917**, respiration is compared to a target parameter. Baroreflex stimulation is increased at **1918** if respiration is below the target and is decreased at **1919** if respiration is above the target. According to various embodiments, the stimulation is not changed if the respiration falls within a blanking window. Various embodiments use memory to provide a hysteresis effect to stabilize the applied stimulation and the baroreflex response. Additionally, in various embodiments, the respiration target is modified during the therapy based on various factors such as the time of day or activity level. At **1920**, it is determined whether to continue with the baroreflex therapy algorithm based on, for example, sensed parameters or the receipt of an event interrupt. If the baroreflex algorithm is to continue, then the process returns to **1917** where respiration is again compared to a target parameter; else the baroreflex algorithm is discontinued at **1921**.

[**0101**] Modulation of Baroreflex Stimulation Based on Adverse Event

[**0102**] Aspects of the present subject matter include a method of automatically increasing baroreceptor stimulation upon detection of an adverse cardiac event to increase vasodilatory response and potentially prevent or reduce myocardial ischemic damage. Various embodiments include a feedback mechanism in a cardiac rhythm management device (such as a pacemaker, AICD or CRT device), which also has a stimulation lead for electrically stimulating baroreceptors. The device monitors cardiac electrical activity through existing methods. In the event of an adverse cardiac event such as ventricular fibrillation (VF) and atrial fibrillation (AF), ventricular tachycardia (VT) and atrial tachycardia (AT) above a predefined rate, and dyspnea as detected by a minute ventilation sensor, angina, decompensation and ischemia, the device responds by increasing baroreceptors stimulation to the maximally allowable level. As a result, blood pressure is temporarily lowered, potentially preventing or reducing myocardial damage due to ischemia. The functionality of a device to treat hypertension can be expanded if it can respond to adverse cardiac events by temporarily modulating the extent of baroreceptors stimulation. Event detection algorithms automatically modulate baroreceptors stimulation, allowing an implantable AHT device to respond to an adverse event by increasing baroreceptors stimulation, potentially preventing or reducing myocardial ischemic damage.

[**0103**] **FIGS. 20A-20B** illustrate methods for modulating baroreceptor stimulation based on detection of an adverse event, according to various embodiments of the present subject matter. The adverse event can be determined by a CRM device, an NS device, or an implantable device with NS/CRM capabilities. **FIG. 20A** illustrates one embodiment for modulating baroreceptor stimulation based on detection of an adverse event. At **2090**A, it is determined whether an adverse event has been detected. If an adverse event has not been detected, normal baropacing (baropacing according to a normal routine) is performed at **2091**A. If an adverse event has been detected, enhanced baropacing is performed at **2092**. In various embodiments, the maximum allowable baropacing is performed when an adverse event is detected. Other baropacing procedures can be implemented. For example, various embodiments normally apply baropacing stimulation and withholds baropacing therapy when an adverse event is detected, and various embodiments normally withhold baropacing therapy and apply baropacing stimulation when an adverse event is detected. **FIG. 20B** illustrate on embodiment for modulating baroreceptor stimulation based on detection of an adverse event. At **2090**B, it is determined whether an adverse event has been detected. If an adverse event has not been detected, normal baropacing (baropacing according to a normal routine) is performed at **2091**B. If an adverse event has been detected, the event is identified at **2093**, and the appropriate baropacing for the identified adverse event is applied at **2094**. For example, proper blood pressure treatment may be different for ventricular fibrillation than for ischemia. According to various embodiments, the desired baropacing is tuned for the identified event at **2095**. For example, one embodiment compares an acquired parameter to a target parameter at **2096**. The baropacing can be increased at **2097** or decreased at **2098** based on the comparison of the acquired parameter to the target parameter.

[**0104**] According to various embodiments, an adverse event includes detectable precursors, such that therapy can be applied to prevent cardiac arrhythmia. In some embodiments, an adverse event includes both cardiac events and non-cardiac events such as a stroke. Furthermore, some embodiments identify both arrhythmic and non-arrhythmic events as adverse events.

[**0105**] Modulation of Baroreflex Stimulation Based on Circadian Rhythm

[**0106**] An aspect of the present subject matter relates to a method for stimulating the baroreflex in hypertension patients so as to mimic the natural fluctuation in blood pressure that occurs over a 24-hour period. Reflex reduction in hypertension is achieved during long-term baroreceptor stimulation without altering the intrinsic fluctuation in arterial pressure. According to various embodiments, an implantable device is designed to stimulate baroreceptors in the carotid sinus, pulmonary artery, or aortic arch using short, high-frequency bursts (such as a square wave with a frequency within a range from approximately 20-150 Hz), for example. Some embodiments directly stimulate the carotid sinus nerve, aortic nerve or vagus nerve with a cuff electrode. However, the bursts do not occur at a constant rate. Rather the stimulation frequency, amplitude, and/or burst frequency rises and falls during the day mimicking the natural circadian rhythm.

[**0107**] Thus, various embodiments of a NS device accounts for natural fluctuations in arterial pressure that occur in both normal and hypertensive individuals. Aside from activity-related changes in mean arterial pressure, subjects also exhibit a consistent fluctuation in pressure on a 24-hour cycle. A device which provides periodic baroreceptor stimulation mimics the intrinsic circadian rhythm, allowing for reflex inhibition of the systematic nervous system and reduced systemic blood pressure without disturbing this rhythm. The present subject matter provides a pacing protocol which varies the baroreceptor stimulation

frequency/amplitude in order to reduce mean arterial pressure without disturbing the intrinsic circadian rhythm.

[0108] **FIGS. 21A-21E** illustrate circadian rhythm. **FIG. 21A** illustrates the circadian rhythm associated with mean arterial pressure for 24 hours from noon to noon; **FIG. 21B** illustrates the circadian rhythm associated with heart rate for 24 hours from noon to noon; **FIG. 21C** illustrates the circadian rhythm associated with percent change of stroke volume (SV %) for 24 hours from noon to noon; **FIG. 21D** illustrates the circadian rhythm associated with the percent change of cardiac output (CO) for 24 hours from noon to noon; and **FIG. 21E** illustrates the circadian rhythm associated with percent change of total peripheral resistance (TPR %), an index of vasodilation, for 24 hours from noon to noon. Various embodiments graph absolute values, and various embodiments graph percent values. In these figures, the shaded portion represents night hours from about 10 PM to 7 AM, and thus represents rest or sleep times. Referring to **FIGS. 21A and 21B**, for example, it is evident that both the mean arterial pressure and the heart rate are lowered during periods of rest. A higher blood pressure and heart rate can adversely affect rest. Additionally, a lower blood pressure and heart rate during the day can adversely affect a person's level of energy.

[0109] Various embodiments of the present subject matter modulate baroreflex stimulation using a pre-programmed template intended to match the circadian rhythm for a number of subjects. Various embodiments of the present subject matter generate a template customized to match a subject.

[0110] **FIG. 22** illustrates a method for modulating baroreceptor stimulation based on circadian rhythm, according to various embodiments of the present subject matter, using a customized circadian rhythm template. The illustrated method **2222** senses and records parameters related to hypertension at **2223**. Examples of such parameters include heart rate and mean arterial pressure. At **2224**, a circadian rhythm template is generated based on these recorded parameters. At **2225**, the baroreflex stimulation is modulated using the circadian rhythm template generated in **2224**.

[0111] Modulation of Baroreflex Stimulation to Provide Desired Cardiac Output

[0112] An aspect of the present subject matter relates to an implantable medical device that provides NS therapy to lower systemic blood pressure by stimulating the baroreflex, and further provides cardiac pacing therapy using a cardiac pacing lead for rate control. Baroreflex stimulation and cardiac pacing occurs in tandem, allowing blood pressure to be lowered without sacrificing cardiac output.

[0113] According to various embodiments, a baroreflex stimulator communicates with a separate implantable CRM device, and uses the existing pacing lead. In various embodiments, baroreflex stimulation occurs through baroreceptors in the pulmonary artery, carotid sinus, or aortic arch with an electrode placed in or adjacent to the vessel wall. In various embodiments, afferent nerves such as the aortic nerve, carotid sinus nerve, or vagus nerve are stimulated directly with a cuff electrode.

[0114] Baroreflex stimulation quickly results in vasodilation, and decreases systemic blood pressure. To compensate for the concurrent decrease in cardiac output, the pacing rate is increased during baroreflex stimulation. The present subject matter allows blood pressure to be gradually lowered through baroreflex stimulation while avoiding the drop in cardiac output that otherwise accompanies such stimulation by combining baroreflex stimulation with cardiac pacing, allowing an implantable device to maintain cardiac output during blood pressure control.

[0115] **FIG. 23A**-B illustrate methods for modulating baroreceptor stimulation based on a cardiac output parameter, according to various embodiments of the present subject matter. **FIG. 23A** illustrates one embodiment for modulating baroreceptor stimulation based on a cardiac output parameter. In the illustrated process **2326**A, it is determined whether baroreflex stimulation is being applied at **2327**. If baroreflex stimulation is not being applied, the present subject matter implements the appropriate pacing therapy, if any, at **2328** with the appropriate pacing rate. If baroreflex stimulation is not being applied, the present subject matter implements a pacing therapy at **2329** with a higher pacing rate to maintain cardiac output.

[0116] **FIG. 23B** illustrates one embodiment for modulating baroreceptor stimulation based on a cardiac output parameter. In the illustrated process **2326**B, baroreflex stimulation is applied at **2330**, and it is determined whether the cardiac output is adequate at **2331**. Upon determining that the cardiac output is not adequate, the pacing rate is increased at **2332** to maintain adequate cardiac output.

[0117] According to various embodiments, an existing pacing rate is increased by a predetermined factor during baroreflex stimulation to maintain cardiac output. In various embodiments, a pacing rate is initiated during baroreflex stimulation to maintain cardiac output. Modulating baroreflex stimulation to provide desired cardiac output can be implemented with atrial and ventricular rate control, AV delay control, resynchronization, and multisite stimulation. Alternatively, the stroke volume may be monitored by right ventricular impedance using electrodes within the right ventricular cavity or by left ventricular impedance using electrodes within or spanning the left ventricular cavity, and the pacing rate may be increased using application of neural stimulation to maintain a fixed cardiac output.

[0118] Modulation of Baroreflex Stimulation to Remodel Stiffening Process

[0119] Aspects of the present subject matter involve a method for baroreflex stimulation, used by an implantable NS device, to lower systemic blood pressure in patients with refractory hypertension. A baroreflex stimulation algorithm gradually increases baroreflex stimulation to slowly adjust blood pressure towards a programmable target. This algorithm prevents the central nervous system from adapting to a constant increased level of baroreflex stimulation, which ordinarily attenuates the pressure-lowering effect. In addition, the gradual nature of the blood pressure change allows the patient to better tolerate the therapy, without abrupt changes in systemic blood pressure and cardiac output.

[0120] The present subject matter provides a specific algorithm or process designed to prevent central nervous system adaptation to increased baroreflex stimulation, to slowly decrease blood pressure levels with time to enable for the reversion of the arterial stiffening process triggered by the previous hypertensive state present in the patient, and to

prevent cardiac output decreases during baroreceptor stimulation. It is expected that, with time, the arterial system reverse remodels the stiffening process that was started by the previously present hypertension. The slow and progressive lowering of the mean/median blood pressure enables the slow reversion of this stiffening process through the reverse remodeling. Blood pressure is reduced without compromising cardiac output in the process, thus avoiding undesired patient symptoms.

[0121] In various embodiments, the device stimulates baroreceptors in the pulmonary artery, carotid sinus, or aortic arch with an electrode placed in or adjacent to the vessel wall. In various embodiments afferent nerves such as the aortic nerve, carotid sinus nerve, or vagus nerve are stimulated directly with a cuff electrode. The stimulated baroreflex quickly results in vasodilation, and a decrease in systemic blood pressure. However, rather than stimulating the baroreflex at a constant, elevated level, the device of the present subject matter initially stimulates at a slightly increased level, and then gradually increases the stimulation over a period of weeks or months, for example. The rate of change is determined by the device based on current and target arterial pressure. In various embodiments, the system determines the rate of change based on direct or indirect measurements of cardiac output, to ensure that the decrease in pressure is not occurring at the expense of a decreased cardiac output. In various embodiments, the rate of baroreflex stimulation is not constant but has a white noise type distribution to more closely mimic the nerve traffic distribution. By mimicking the nerve traffic distribution, it is expected that the baroreflex is more responsive to the stimulation, thus lowering the threshold for stimulating the baroreflex.

[0122] **FIG. 24** illustrates a method for modulating baroreceptor stimulation to reverse remodel stiffening, according to various embodiments of the present subject matter. A baroreflex event trigger occurs at **2433**. This trigger includes any event which initiates baroreflex stimulation, including the activation of an AHT device. At **2434**, an algorithm is implemented to increase baroreflex stimulation by a predetermined rate of change to gradually lower the blood pressure to a target pressure in order to reverse remodel the stiffening process. At **2435**, it is determined whether to continue with the baroreflex stimulation algorithm. The algorithm may be discontinued at **2436** based on an event interrupt, sensed parameters, and/or reaching the target blood pressure, for example. At **2437**, it is determined whether the cardiac output is acceptable. If the cardiac output in not acceptable, at **2438** the rate of change for the baroreflex stimulate is modified based on the cardiac output.

[0123] Baroreflex Stimulation to Treat Myocardial Infarction

[0124] Following a myocardial infarction, myocytes in the infarcted region die and are replaced by scar tissue, which has different mechanical and elastic properties from functional myocardium. Over time, this infarcted area can thin and expand, causing a redistribution of myocardial stresses over the entire heart. Eventually, this process leads to impaired mechanical function in the highly stressed regions and heart failure. The highly stressed regions are referred to as being heavily "loaded" and a reduction in stress is termed "unloading." A device to treat acute myocardial infarction to prevent or reduce myocardial damage is desirable.

[0125] An aspect of the present subject matter relates to an implantable device that monitors cardiac electrical activity. Upon detection of a myocardial infarction, the device electrically stimulates the baroreflex, by stimulating baroreceptors in or adjacent to the vessel walls and/or by directly stimulating pressure-sensitive nerves. Increased baroreflex stimulation compensates for reduced baroreflex sensitivity, and improves the clinical outcome in patients following a myocardial infarction. An implantable device (for example, a CRM device) monitors cardiac electrical activity. Upon detection of a myocardial infarction, the device stimulates the baroreflex. Some embodiments of the device stimulate baroreceptors in the pulmonary artery, carotid sinus, or aortic arch with an electrode placed in or adjacent to the vessel wall. In various embodiments, afferent nerves such as the aortic nerve are stimulated directly with a cuff electrode, or with a lead intravenously placed near the afferent nerve. Afferent nerves such as the carotid sinus nerve or vagus nerve are stimulated directly with a cuff electrode, or with a lead intravenously placed near the afferent nerve. In various embodiments, a cardiac fat pad is stimulated using an electrode screwed into the fat pad, or a lead intravenously fed into a vessel or chamber proximate to the fat pad.

[0126] Baroreflex stimulation quickly results in vasodilation, and a decrease in systemic blood pressure. This compensates for reduced baroreflex sensitivity and reduces myocardial infarction. According to various embodiments, systemic blood pressure, or a surrogate parameter, are monitored during baroreflex stimulation to insure that an appropriate level of stimulation is delivered. Some aspects and embodiments of the present subject matter provides baroreflex stimulation to prevent ischemic damage following myocardial infarction.

[0127] **FIGS. 25A-25B** illustrate a system and method to detect myocardial infarction and perform baropacing in response to the detected myocardial infarction, according to various embodiments of the present subject matter. **FIG. 25A** illustrates a system that includes a myocardial infarction detector **2539** and a baroreflex or baroreceptor stimulator **2540**. A myocardial infarction can be detected using an electrocardiogram, for example. For example, a template can be compared to the electrocardiogram to determine a myocardial infarction. Another example detects changes in the ST segment elevation to detect myocardial infarction. In various embodiments, the detector **2539** and stimulator **2540** are integrated into a single implantable device such as in an AHT device or a CRM device, for example. In various embodiments, the detector **2539** and stimulator **2540** are implemented in separate implantable devices that are adapted to communicate with each other.

[0128] **FIG. 25B** illustrates a method to detect myocardial infarction and perform baropacing in response to the detected myocardial infarction, according to various embodiments of the present subject matter. At **2541**, it is determined whether a myocardial infarction has occurred. Upon determining that a myocardial infarction has occurred, the baroreflex is stimulated at **2542**. For example, in various embodiments, the baroreceptors in and around the pulmonary artery are stimulated using a lead fed through the right atrium and the pulmonary valve and into the pulmonary artery. Other embodiments stimulate other baroreceptor sites and pressure sensitive nerves. Some embodiments monitor the systemic blood pressure or a surrogate parameter at

2543, and determines at **2544** if the stimulation should be adjusted based on this monitoring. If the stimulation is to be adjusted, the baroreflex stimulation is modulated at **2545**. Examples of modulation include changing the amplitude, frequency, burst frequency and/or waveform of the stimulation.

[0129] Neural stimulation, such as baroreflex stimulation, can be used to unload after a myocardial infarction. Various embodiments use an acute myocardial infraction detection sensor, such as an ischemia sensor, within a feedback control system of an NS device. However, a myocardial infraction detection sensor is not required. For example, a stimulation lead can be implanted after a myocardial infarction. In various embodiments, the stimulation lead is implanted through the right atrium and into the pulmonary artery to stimulate baroreceptors in and around the pulmonary artery. Various embodiments implant stimulation cuffs or leads to stimulate afferent nerves, electrode screws or leads to stimulate cardiac fat pads, and leads to stimulate other baroreceptors as provided elsewhere in this disclosure.

[0130] Electrical pre-excitation of a heavily loaded region will reduce loading on this region. This pre-excitation may significantly reduce cardiac output resulting in sympathetic activation and an increase in global stress, ultimately leading to deleterious remodeling of the heart. This process may be circumvented by increased neural stimulation to reduce the impact of this reflex. Thus, activation of the parasympathetic nervous system during pre-excitation may prevent the undesirable side-effects of unloading by electrical pre-excitation.

[0131] One of ordinary skill in the art will understand that, the modules and other circuitry shown and described herein can be implemented using software, hardware, and combinations of software and hardware. As such, the term module is intended to encompass software implementations, hardware implementations, and software and hardware implementations.

[0132] The methods illustrated in this disclosure are not intended to be exclusive of other methods within the scope of the present subject matter. Those of ordinary skill in the art will understand, upon reading and comprehending this disclosure, other methods within the scope of the present subject matter. The above-identified embodiments, and portions of the illustrated embodiments, are not necessarily mutually exclusive. These embodiments, or portions thereof, can be combined. For example, various embodiments combine two or more of the illustrated processes. Two or more sensed parameters can be combined into a composite parameter used to provide a desired neural stimulation (NS) or anti-hypertension (AHT) therapy. In various embodiments, the methods provided above are implemented as a computer data signal embodied in a carrier wave or propagated signal, that represents a sequence of instructions which, when executed by a processor cause the processor to perform the respective method. In various embodiments, methods provided above are implemented as a set of instructions contained on a computer-accessible medium capable of directing a processor to perform the respective method. In various embodiments, the medium is a magnetic medium, an electronic medium, or an optical medium.

[0133] Although specific embodiments have been illustrated and described herein, it will be appreciated by those of ordinary skill in the art that any arrangement which is calculated to achieve the same purpose may be substituted for the specific embodiment shown. This application is intended to cover adaptations or variations of the present subject matter. It is to be understood that the above description is intended to be illustrative, and not restrictive. Combinations of the above embodiments as well as combinations of portions of the above embodiments in other embodiments will be apparent to those of skill in the art upon reviewing the above description. The scope of the present subject matter should be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method for treating disordered breathing in a patient, comprising delivering electrical stimulation therapy that modifies a patient's baroreflex response to treat the disordered breathing.

2. The method of claim 1, wherein delivering the electrical stimulation therapy modifying the patient's baroreflex response comprises delivering the electrical stimulation therapy to treat apnea.

3. The method of claim 1, wherein delivering the electrical stimulation therapy modifying the patient's baroreflex response comprises electrically stimulating one or more baroreceptor sites.

4. The method of claim 1, wherein delivering the electrical stimulation therapy modifying the patient's baroreflex response comprises delivering the electrical stimulation therapy modifying the patient's baroreflex response based on circadian rhythm.

5. The method of claim 1, wherein delivering the electrical stimulation therapy modifying the patient's baroreflex response comprises:

generating a circadian rhythm template; and

modulating the electrical stimulation based on the circadian rhythm template.

6. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on a cardiovascular parameter.

7. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on arterial pressure.

8. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on heart rate.

9. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on stroke volume.

10. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on cardiac output.

11. The method of claim 5, wherein generating the circadian rhythm template comprises generating the circadian rhythm template based on total peripheral resistance.

12. The method of claim 1, wherein delivering electrical stimulation therapy modifying the patient's baroreflex response comprises modulating a parameter of the electrical stimulation therapy.

13. The method of claim 12, wherein modulating the parameter of the electrical stimulation therapy comprises modulating electrical stimulation frequency.

14. The method of claim 12, wherein modulating the parameter of the electrical stimulation therapy comprises modulating electrical stimulation amplitude.

15. The method of claim 12, wherein modulating the parameter of the electrical stimulation therapy comprises modulating electrical stimulation burst frequency.

16. The method of claim 1, wherein delivering the electrical stimulation therapy modifying the patient's baroreflex response comprises delivering the electrical stimulation modifying the patient's baroreflex response to mimic a natural circadian rhythm.

17. A disordered breathing therapy system, comprising:

one or more electrodes configured to deliver an electrical stimulation signal to a region associated with a patient's baroreflex response; and

a pulse generator coupled to the one or more electrodes, the pulse generator configured to control delivery of an electrical stimulation therapy using the one or more electrodes, the electrical stimulation therapy modifying a patient's baroreflex response to treat disordered breathing.

18. The system of claim 17, wherein the pulse generator is configured to treat apnea.

19. The system of claim 17, further comprising a template generator coupled to the pulse generator, the template generator configured to generate a circadian rhythm, wherein the pulse generator is configured to modulate the electrical stimulation therapy using the circadian rhythm template.

20. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on a cardiovascular parameter.

21. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on arterial pressure.

22. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on heart rate.

23. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on stroke volume.

24. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on cardiac output.

25. The system of claim 19, wherein the template generator is configured to generate the circadian rhythm template based on total peripheral resistance.

26. The system of claim 17, wherein the pulse generator is configured to modulate one or more parameters of the electrical stimulation therapy modifying a patient's baroreflex response to treat disordered breathing.

27. The system of claim 26, wherein the one or more parameters comprise a stimulation frequency.

28. The system of claim 26, wherein the one or more parameters comprise a stimulation amplitude.

29. The system of claim 26, wherein the one or more parameters comprise a stimulation burst frequency.

30. The system of claim 17, wherein the pulse generator is configured to modulate the electrical stimulation therapy modifying the patient's baroreflex response to mimic a circadian rhythm.

31. A system for treating disordered breathing in a patient, comprising:

means for delivering electrical stimulation to one or more regions associated with a patient's baroreflex response; and

means for controlling delivery of the electrical stimulation to modify a patient's baroreflex response to treat the disordered breathing.

32. The system of claim 31, further comprising means for modulating the electrical stimulation therapy to mimic a circadian rhythm.

33. The system of claim 31, further comprising means for generating a circadian rhythm template and means for modulating the electrical stimulation therapy using the circadian rhythm template.

34. The system of claim 31, further comprising means for modulating one or more parameters of the electrical stimulation.

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